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CONTENTS OF PREVIOUS NUMBER

MARCH, 1927. NUMBER 3

Effect of Ultraviolet Light on Oxygen Consumption and on Total Metabolism. Edward H. Mason, M.D., Montreal, and Howard H. Mason, M.D., New York.

Carbohydrate Tolerance in Normal Persons and in Nondiabetic Patients. Albert H. Rowe, M.D., and Hobart Rogers, M.D., Oakland, Calif.

Biliary, Pancreatic and Duodenal Studies. Lay Martin, M.D., Baltimore.
II. Estimation of Pancreatic Enzymes and Value of Such Determinations from a Clinical Standpoint.
III. Estimation of Value of Duodenal Drainage for the Diagnosis of Biliary Disease Based on the Examination of Fifty Patients.

Mineral Salt Content of the Blood in Disease. A. S. Blumgarten, M.D., and George L. Rohdenburg, M.D., New York.

Ephedrine: A Clinical Study. William S. Middleton, M.D., and K. K. Chen, Ph.D., Madison, Wis.

Spastic Esophagus and Mucous Colitis: Etiology and Treatment by Progressive Relaxation. Edmund Jacobson, M.D., Chicago.

A Comparative Study of Ephedrine, Pseudo-Ephedrine and β-Phenyl-Ethylamine, with Reference to Their Effects on the Pupil and on the Blood Pressure. K. K. Chen, Ph.D., Madison, Wis.

Glycolysis in Normal and in Leukemic Blood. Mark Falcon-Lesses, M.D. Boston.

The Red Cell Count in Arthritis:
First Paper. E. G. Peirce, M.D., and Ralph Pemberton, M.D., Philadelphia.
Second Paper. Caroline Y. Crouter, M.S., and F. A. Cajori, Ph.D., Philadelphia.

Studies on Peritonitis. Bernhard Steinberg, M.D., and Harry Goldblatt, M.D., Cleveland.
I. Production of Experimental Peritonitis and Survival Following Intraperitoneal Injection of Bacillus Coli.
II. Passage of Bacteria from the Peritoneal Cavity into Lymph and Blood.

Spleens from Gaucher's Disease and Lipoid-Histiocytosis: The Chemical Analysis. William Bloom, M.D., and Ruth Kern, M.S., Chicago.

Book Reviews.

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Archives of Internal Medicine

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HYPERTENSION IN PREGNANCY

RELATION OF THE CALCIUM CONTENT OF THE BLOOD TO THE ETIOLOGY *

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CHICAGO

A thorough analysis of the theories of the etiology of hypertension will not be undertaken in this article. In all probability the etiology of vascular disease varies in different cases and is the result of a combination of insults to the circulatory apparatus.[1] With the field limited to the hypertensions occurring in pregnancy, still another set of theories has been evolved,[2] the gist of which is the view that hypertension in pregnancy is a manifestation of the reaction to an intoxication. The exact nature and source of the toxemia is still unknown.[3]

Lange [4] and others,[5] and more recently Strouse and Daly,[6] have emphasized the importance of thyroid intoxications in pregnancy. That the parathyroid glands should be similarly upset is not unlikely. It is well known that in parathyroprivia an increased muscular tone is evident.[7] Associated with this phenomenon is a lowered concentration of calcium in the blood, first pointed out by Salvesen,[8] and since confirmed by numerous investigators.[9] Collip and his co-workers [10] have

* From the medical clinic of the Chicago Lying-In Hospital and Dispensary, aided by a grant from the Mothers' Aid Society.

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10. Collip, J. B.: J. Biol. Chem. **63**:395 (March) 1925. Collip, J. B., and Clark, E. P.: J. Biol. Chem. **63**:461 (March) 1925. Collip, J. B.; Clark, E. P., and Scott, J. W.: J. Biol. Chem. **63**:439 (March) 1925. Berman, L.: J. Lab. & Clin. Med. **11**:412 (Feb.) 1926.

demonstrated an active parathyroid hormone capable of elevating the blood calcium content.[11] This hormone is so potent that its use should be attended with great caution, as an excess may give rise to a dangerous hypercalcemia.[12] Engelbach [13] believed in a physiologic relationship between hypocalcemia, parathyroid deficiency and hypertension. Kylin [14] and his co-workers [15] and Reid [16] have presented evidence that there is a distinct relationship between a hypocalcemia and an elevation of the blood pressure. Kylin also observed a hypercalcemia in diabetes with hypotension.[17] Schmitz, Rohdenburg and Myers [18] and Anderson [19] demonstrated a low calcium concentration in chronic nephritis with hypertension.

Furthermore, during pregnancy there is an active calcium anabolism in the fetus with a corresponding drain on the maternal blood and tissue calcium.[20] Previous reports on the status of calcium of the blood in pregnancy have been somewhat conflicting. Handelman, Rose and Sherwin [21] found the concentration normal but lowered after parturition. That this fall is not due to the hemorrhage attendant on the delivery is shown by the results of Swingle and Werner,[22] who showed that bleeding caused a rise in the blood calcium with a transient disappearance of tetany in parathyroidectomized dogs. Feinberg and Lash [23] in a short series of eclamptic and control cases could demonstrate no relationship between the blood calcium content and the convulsions.

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16. Reid, W. D.: Boston M. & S. J. **192**:883 (May 7) 1925.

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19. Anderson, W. T.: Hospitalstid. **68**:1177, 1925.

20. The Need of Calcium, editorial, J. A. M. A. **85**:1065 (Oct. 3) 1925.

21. Handelman, I.; Rose, A., and Sherwin, C. P.: Blood Changes in Antepartum and Postpartum Period of Young Mothers, Arch. Int. Med. **37**:725 (May) 1926.

22. Swingle, W. W., and Werner, W. F.: Am. J. Physiol. **65**:372 (Jan.) 1926.

23. Feinberg, S. M., and Lash, A. F.: Surg. Gynec. Obst. **42**:255 (Feb.) 1926.

Hypocalcemia has been demonstrated in other states of smooth muscle spasticity, such as pertussis,[24] asphyxia [25] and asthma.[26] There is some contradiction to this in pertussis.[27] Anderson and Graham [28] assert that tetany in babies is not parallel to a hypocalcemia but is associated with an alkalosis. A hypercalcemia is present in suppurating infections [29] and gout.[30] Late tuberculosis is associated with hypocalcemia [31] and is said to be benefited by therapy with calcium chloride.

Evidence has been presented which indicates that a metabolic disturbance associated with a hypocalcemia may be one etiologic factor in hypertension and in other conditions of increased smooth muscle tonus. If this is the case, the hypocalcemia should be most conspiciously manifest in the hypertensions of pregnancy, in which condition a maternal depletion of calcium takes place. That the parathyroid glands are intimately associated with calcium metabolism is clearly demonstrable. A relatively comprehensive objective study of the blood pressure and blood calcium determinations in a series of pregnant women was therefore undertaken to determine, if possible, any relationship between the two phenomena.

METHODS

The present investigation deals with the results obtained in 222 blood calcium determinations from a series of cases, including normal pregnant patients, pregnant patients with hypertension, and also some nonpregnant controls. The arterial tension was observed in each instance at the time the blood specimens were obtained. The analytic method was that developed by Tisdall,[32] modified by Clark and Collip [33] and later by Tweedie.[34] So far as possible the specimen and arterial tension readings were obtained at a uniform time of day, usually in the midafternoon.

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24. Powers, G. F.: Tetany as a Cause of Convulsions in Whooping Cough, Am. J. Dis. Child. **30**:632 (Nov.) 1925.

25. Binet, L., and Blanchetiere, A.: Compt. rend Soc. de biol. **93**:511 (July 24) 1925.

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27. Regan, J. C., and Tolstouhov, A.: Significance of Blood Chemical Changes in Pertussis, J. A. M. A. **86**:1116 (April 10) 1926.

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29. Schulze, F., and Scheller, E.: Arch. f. klin. Chir. **136**:763, 1925.

30. Horowitz, P.: Am. J. M. Sc. **171**:560 (April) 1926.

31. Teplitz, M. M.: Am. Rev. Tuberc. **7**:222 (Nov.) 1925. Schoenheit, E. W.: Am. J. M. Sc. **170**:689 (Nov.) 1925. Pinkhof, J.: Nederl. Tijdschr. v. Geneesk. **1**:230 (Jan. 16) 1926. Piñerua, O.: Med. Ibera **20**:98, 1926.

32. Kramer, B., and Tisdall, F. F.: Bull. Johns Hopkins Hosp. **32**:44 (Feb.) 1921. Kramer, B.; Tisdall, F. F., and Howland, J.: Calcium and Phosphorus in Serum in Relation to Rickets, Am. J. Dis. Child. **22**:560 (Dec.) 1921. Kramer, B., and Tisdall, F. F.: J. Biol. Chem. **47**:475 (Aug.) 1921. Tisdall, F. F.: J. Biol. Chem. **56**:439 (June) 1923.

33. Clark, E. P., and Collip, J. B.: J. Biol. Chem. **63**:461 (March) 1925.

34. Tweedie: To be published.

Hypertension cases in pregnancy may be grouped into four divisions,[35] as follows:

1. A relatively benign type, occurring moderately early in pregnancy, characterized by a gradual rise in arterial tension and little evidence of serious intoxication. These are the so-called nephroses of pregnancy.

2. A late malignant type, occurring with a sudden unheralded onset, a rapid rise in arterial tension and evidences of marked intoxication, quickly becoming a true eclampsia, with hepatic as well as renal and vascular damage.

TABLE 1.—*Relation of Average Blood Pressures at Varying Levels of Calcium Concentration*

Blood Calcium, Mg. per 100 Cc.	Average Blood Pressure		Number of Observations
	Systolic	Diastolic	
6- 7	148	96	7
7- 8	142	87	8
8- 9	150	93	10
9-10	148	91	39
10-11	150	93	64
11-12	143	88	62
12-13	144	90	22
13-14	155	96	10
Total			222

TABLE 2.—*Relation of Blood Calcium Concentration at Varying Blood Pressures*

Systolic Blood Pressure, Mm. Mercury	Average Blood Calcium	Number of Observations
90 - 100	12.1	2
100 - 110	10.7	10
110 - 120	10.7	24
120 - 130	11.1	25
130 - 140	10.5	23
140 - 150	10.3	34
150 - 160	10.1	37
160 - 170	10.6	24
170 - 180	10.1	15
180 - 190	10.9	13
190 - 200	11.1	3
200 - 210	11.2	7
210 - 220	12.4	1
220 - 230	11.8	2
230 - 240	9.8	2
Total		222

3. Hypertension in pregnancy in patients with preexisting vascular and usually renal disease, both undergoing exacerbation during the pregnancy.

4. Hypertension in pregnancy with definite complications, such as toxic goiter, cardiac disease, acute infections and the like.

The present series included twenty-nine cases of the first type, only one of the second or eclamptic group, sixteen of the third group, and one of the fourth. Four cases were classified as falling into both groups 1 and 3. Forty cases were studied as controls, including both the pregnant and the nonpregnant without hypertension.

35. Stieglitz, E. J.: Illinois M. J. **50**:234 (Sept.) 1926.

RESULTS

The comparison of the arterial tension levels to the calcium content of the blood may be carried out by two methods: first, to determine the average arterial tension at given blood calcium concentrations and,

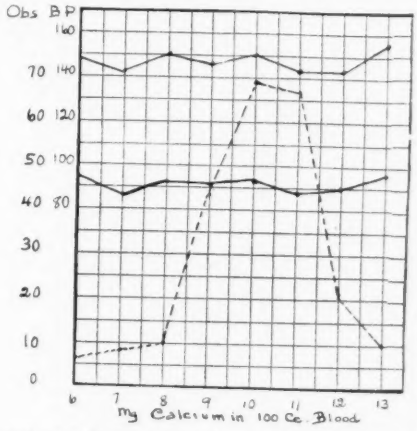

Chart 1.—Average arterial tension at given blood calcium concentrations: upper solid line, systolic; lower solid line, diastolic blood pressures; broken line, number of observations.

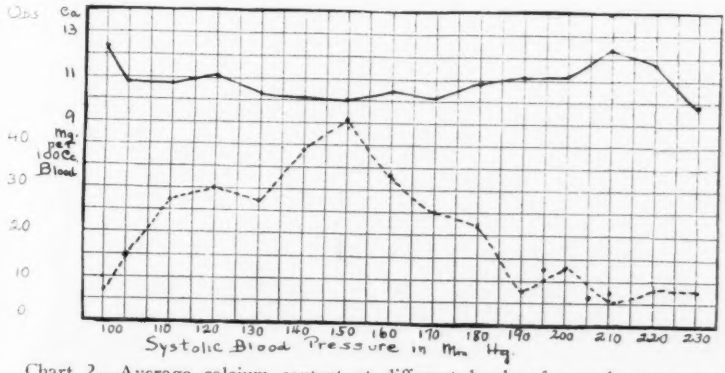

Chart 2.—Average calcium content at different levels of vascular pressure: solid line, blood calcium content; broken line, number of observations.

second, to determine the average calcium content at different levels of vascular pressure. The results of such analyses appear in tables 1 and 2 and charts 1 and 2, incorporating all the determinations.

The tabulated and charted results reveal a definite lack of direct or indirect variation. The averages are remarkably uniform in either

method of comparison. The averages of the blood calcium content coincide well with previously published results for normal persons.[36] Eighty-eight per cent of the calcium determinations ranged from 9 to

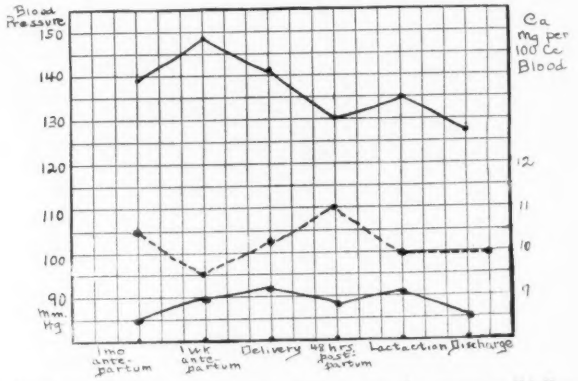

Chart 3.—Curves of twenty-five cases from group 1: upper solid line, systolic, lower solid line, diastolic blood pressures; broken line, blood calcium content.

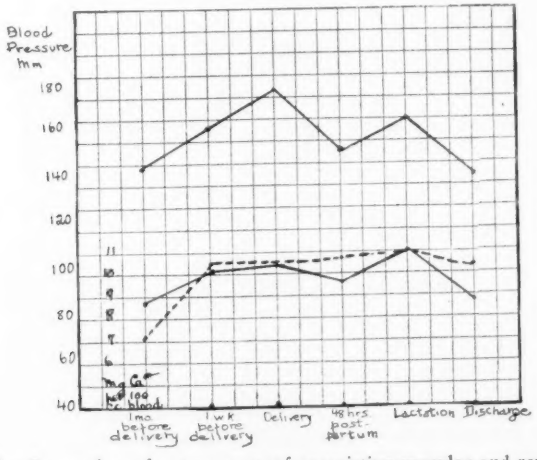

Chart 4.—Curves from fourteen cases of preexisting vascular and renal disease: upper solid line, systolic, lower solid line, diastolic blood pressures; broken line, calcium content.

13 mg. per hundred cubic centimeters of plasma, and 60 per cent fell between 10 and 12 mg. Anderson [19] places the normal average at 10.7 mg. per hundred cubic centimeters of plasma. Pozzi [37] found no

36. Wyss, E.: Blood Calcium, Geneva letter, J. A. M. A. **86**:1783 (June 5) 1926.
37. Pozzi, A.: Policlinico **32**:503 (Oct.) 1925.

parallelism between the blood pressure and blood calcium in dogs after irradiation of the suprarenals. These results are essentially similar to those of Feinberg and Lash [23] in eclamptic cases.

However, averages of large series of figures are prone to obliterate fluctuations and therefore distort or conceal some true relationships. In

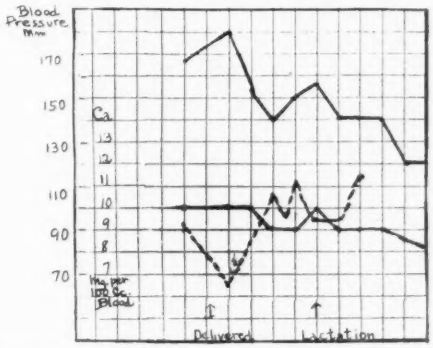

Chart 5.—Record of patient HC 15: upper solid line, systolic, lower solid line, diastolic blood pressures; broken line, calcium content.

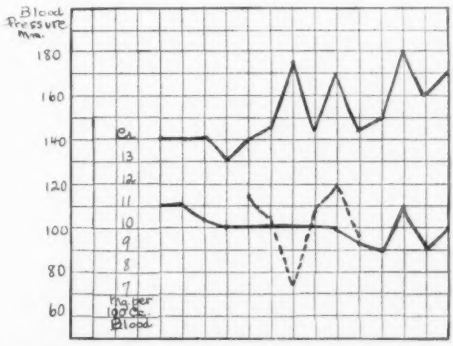

Chart 6.—Record of patient HC 19 during pregnancy: upper solid line, systolic, lower solid line, diastolic blood pressures; broken line, calcium content.

the course of these studies it was noted that a prompt postpartum fall in blood pressure occurred followed by a secondary rise with surprising regularity. The secondary rise occurred from fifty to one hundred hours after delivery and was coincident with the onset and establishment of lactation. In order to limit the study to one type of disturbance, data from twenty-five cases of the first group were tabulated. The results are given in chart 3.

These observations are of physiologic interest. They correspond to the results of Hetenyi,[38] who states that the blood calcium falls near the end of pregnancy. The analysis of the total averages demonstrated an absence of definite parallelism between a rising arterial tension and a diminishing calcium concentration in the blood. Therefore, in pregnancy at any rate, I am led to the conclusion that the latter factor is not a vital mechanism in the etiology of hypertension. However, in the third chart there is clearly an inverse relation between the arterial tension and the blood calcium. Particularly interesting is the rise in tension, with the corresponding moderate hypocalcemia which occurred so regularly coincident with the onset of lactation. That a physiologic relation exists is highly probable, especially in view of the fact that lactation brings about a sudden drain on the free circulating calcium, which is then more slowly compensated by a metabolic readjustment. In the group of fourteen cases with preexisting vascular and renal disease a similar curve was obtained, although there was no definite relationship to the calcium content of the blood (chart 4).

Another noticeable difference is the greater height of both the systolic and the diastolic averages. This is characteristic of the group; those patients with vascular disease existing before their pregnancy may, and usually do, have blood pressures so high that ignorance of the preexisting disease may cause great alarm.

Two charts of individual cases (HC 15 and HC 19) reveal a similar parallelism between an elevation in arterial tension and a hypocalcemia. Other cases showed no such association.

The greatest degree of hypocalcemia occurred in a case of severe chronic glomerular nephritis with moderate hypertension, both conditions being aggravated markedly by the pregnancy.

COMMENT

These investigations demonstrate a lack of constant variation between the calcium concentration of the blood plasma and the arterial tension and reveal relatively normal calcium values irrespective of hypertension in pregnancy. Therefore, the conclusion that hypocalcemia is not a major etiologic factor in pathologic hypertension is warranted. However, a clear relationship exists between minor variations in arterial tension and the blood calcium content. This is strikingly demonstrated in chart 3. Such a relation has considerable physiologic significance and coincides with many previous observations of a relative hypocalcemia in clinical states associated with an increased tone of smooth muscle fibers. That the appearance of the secondary rise in arterial tension and fall in calcium content simultaneously with the onset of

38. Hetenyi and Liebmann: Med. Klin. **21**:1929, 1925.

lactation is more than purely coincidental is highly probable. The sudden drain on free blood and tissue calcium, with the resultant hypocalcemia, explains this phenomenon. The occurrence of physiologic variations in blood pressure is not necessarily due to the same mechanism as pathologic hypertension.

Therapeutically numerous attempts have been made to cause an increase in the blood calcium. Addison and Clark [39] report a fall in arterial tension, associated with diuresis and acidosis on the administration of calcium and potassium chlorides. Singer and others [40] similarly report a fall in the blood pressure, a slowing of the cardiac rate and diuresis following the therapeutic use of calcium lactate. However, it must be recalled that calcium slows the heart and that this in itself may be the explanation of the falling blood pressure. Hjort [41] showed calcium salts to be absorbed on administration by mouth, but Orr, Holt, Wilkins and Boone [42] and Briggs [43] demonstrated that this caused a reduction of the amount of phosphate in the blood and urine, by the precipitation of calcium phosphate in the bowel. Briggs emphasized that this reduces the synthesis of ammonia by the kidney, thereby reducing the renal load. However, in the absence of evidence that hypocalcemia is the fundamental cause of the hypertension, therapy directed toward raising the level of the blood calcium is not strongly indicated. True, pregnancy is associated with a maternal depletion of calcium, which must be replaced. Dietary management, however, suffices for this.

The observations of Rémond [44] that calcium concentration falls during active growth of cancer cells and rises during regression is of interest in connection with rapid fetal growth, with the gradually increasing moderate hypocalcemia near the termination of pregnancy, and the rise again during uterine involution.

SUMMARY

Hypocalcemia is not of major etiologic significance in arterial hypertension in pregnancy, despite the fact that in such cases the relationship should be most conspicuous.

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39. Addison, W. L. T., and Clark, H. G.: Canad. M. A. J. **15**:913 (Sept.) 1925.

40. Singer, G.: Wien. med. Wchnschr. **34**:247, 1921. Loewenstein, W.: Klin. Wchnschr. **5**:354 (Feb. 26) 1926.

41. Hjort, A. M.: J. Biol. Chem. **45**:783 (Oct.) 1925.

42. Orr, W. J.; Holt, L. E., Jr.; Wilkins, L., and Boone, F. H.: Relation of Calcium and Phosphorus in Diet to Absorption of These Elements from Intestine, Am. J. Dis. Child. **28**:574 (Nov.) 1924.

43. Briggs, A. P.: Metabolic Aspects of Calcium Therapy, Arch. Int. Med. **37**: 440 (March) 1926.

44. Rémond, A.: Compt. rend. Soc. de biol. **93**:1061, 1925.

During the final month of pregnancy a gradual rise in arterial tension is associated with a moderate hypocalcemia.

Immediately after parturition a fall in blood pressure occurs, with a corresponding rise in the blood calcium concentration.

Coincident and probably associated with the onset of lactation a secondary elevation in arterial tension occurs, with a corresponding and equally transient hypocalcemia.

The latter phenomenon permits of physiologic interpretation.

VITAL CAPACITY

A STUDY OF THE EFFECT OF BREATHING DRY AIR *

R. D. LEAS, M.D.
CLEVELAND

It has been recognized that climates with a low relative humidity give relief to some patients with asthma. Inferentially this is due, at least in part, to the beneficial effect of dry air, which will extract more moisture from the bronchial tree than the air of a locality with a higher humidity. If this is true in respect to the bronchial moisture of asthma, it should also be true in respect to bronchial moisture from other sources, such as cardiac and renal.

The possible significance of this factor was seen in the course of experimentation on an entirely different problem. It happened that a patient with cardiac decompensation was asked to inspire through a jar of calcium chloride for a five minute period. The patient expressed his gratitude for the procedure because he felt so much better and could breathe more easily than before. The experimenters' curiosity being aroused, a number of patients with asthmatic, cardiac and renal diseases and a few with pulmonary infiltration were examined. A second series of one hundred patients, normal as to heart and lungs, served as a control.

The method consisted simply of taking the vital capacity on the Sanborn-Benedict metabolimeter before and after the patient breathed through a jar containing anhydrous calcium chloride. Three vital capacity readings were taken before and three after the breathing of dry air, and the highest of these was recorded in each instance. The chloride jar was connected to a face mask equipped with two-way valves so that only the inspired air passed through the jar. Expired air is presumably always saturated with moisture at body temperature. In breathing, dry air will extract more moisture from the bronchi than will room air, which already contains a certain amount of moisture. The amount of moisture in the expired air is not appreciably changed after dry air is discontinued, as shown by the following experiment. The amount of water collected in calcium chloride from the expired air before breathing dry air was 1.430 Gm. per 25 liters, and after discontinuing dry air, 1.335 Gm. Carbon dioxide is not combined with calcium chloride; therefore it is a negligible factor.

The results obtained in the normal subjects are shown in table 1. There was an average increase of vital capacity of 12.5 cc., or 0.3 per cent after breathing dry air. Forty-four per cent of the patients

* From the Department of Medicine of Western Reserve University and Lakeside Hospital.

responded with an increase of vital capacity. Of these, 45 per cent showed an increase from 110 to 308 cc., and 55 per cent, less than 100 cc. Fifteen per cent of the entire series showed no change after breathing dry air, and 41 per cent responded with a decrease of vital capacity. Of these, 14 per cent gave a decrease from 110 to 308 cc., and 86 per cent less than 100 cc. It will be noted that the greatest increase was 308 cc., or 8.4 per cent., and the greatest decrease likewise was 308 cc., or 7.6 per cent. Although 75 per cent of the patients showed no change after breathing dry air or varied to ± 100 cc., the change in the remaining 25 per cent requires explanation.

In this kind of an experiment, in which the personal factor is such an important element, it is hard to estimate when a patient has given his best cooperation. Some patients are overanxious to please while others are the reverse, and the results may be equally unreliable. Such factors may account for variations as great as 308 cc. On several occasions I became the subject, and an assistant found that my vital capacity remained exactly the same after breathing dry air. In these instances cooperation is not so questionable. There is another explanation which may be offered for those who gave a decrease of vital capacity after breathing dry air; namely, superventilation, which has been shown by Joannides [1] to decrease vital capacity. The patients were instructed to breathe normally, but in several instances respiration was deeper and more rapid than normal.

The criticisms mentioned above are applicable to the patients with bronchiolar edema, but in these cases there were criteria to prove the benefit of breathing dry air in addition to an increase of vital capacity. The least important of these criteria was the subjective improvement noted by a large proportion of the patients. In some cases this may have been influenced by suggestion, but in a number it was purely spontaneous. Most important, however, were the observations of physical signs before and after the experiment. If a patient experienced relief, almost invariably some change was noted in the number and character of the râles in the lungs; still more important, change was noted in the respiratory excursion of the chest and the lung volume.

The significance of the respiratory excursion of the chest has been pointed out by Hoover [2] and is particularly significant when properly applied in a study of these cases. He has shown that the movement of the costal margins during inspiration results from the combined effect of the intercostal muscles and the diaphragm. The effect of the intercostal muscles is to produce lateral movement of the rib ends and

1. Joannides, M.: Effect of Dyspnea Variously Produced on Vital Capacity of Lungs, Arch. Int. Med. **33**:145 (Jan.) 1924.

2. Hoover, C. F.: Diagnostic Lung Signs, Arch. Int. Med. **20**:701 (Nov.) 1917.

TABLE 1.—*Normal Cases*

Case	Vital Capacity Before Dry Air, Cc.	Vital Capacity After Dry Air, Cc.	Expected Vital Capacity, Cc.	Gain or Loss in Cc.	Gain or Loss in Percentage
1	4,750	4,730	4,400	— 20	—0.4
2	4,730	4,884	4,652	+154	+3.3
3	3,894	3,982	4,025	+ 88	+2.3
4	3,938	4,070	3,925	+132	+3.4
5	3,828	3,872	4,175	+ 44	+1.1
6	5,280	5,236	5,000	— 44	—0.8
7	4,576	4,444	4,375	—132	—2.9
8	4,752	4,730	4,350	— 22	—0.4
9	3,432	3,520	4,075	+ 88	+2.6
10	4,664	4,708	4,072	+ 44	+0.9
11	4,730	4,708	4,750	— 22	—0.4
12	3,696	3,652	3,850	— 44	—1.2
13	4,554	4,796	4,450	+242	+5.3
14	3,586	3,586	3,040	0	0.0
15	2,904	2,970	3,340	+ 66	+2.2
16	2,596	2,618	.....	+ 22	+0.8
17	5,390	5,610	4,725	+220	+4.1
18	3,344	3,488	3,900	+144	+4.3
19	3,300	3,300	.....	0	0.0
20	5,236	5,170	.....	— 66	—1.2
21	3,872	3,850	4,225	— 22	—0.5
22	3,564	3,564	4,200	0	0.0
23	2,838	2,816	2,860	— 22	—0.7
24	4,466	4,466	4,550	0	0.0
25	3,476	3,432	3,975	— 44	—1.2
26	2,750	2,750	2,820	0	0.0
27	2,442	2,442	2,790	0	0.0
28	3,080	2,904	2,808	—176	—5.7
29	4,444	4,532	4,370	+ 88	+1.9
30	4,686	4,730	4,300	+ 44	+0.9
31	4,334	4,400	4,275	+ 66	+1.5
32	4,994	4,972	4,925	— 22	—0.4
33	3,036	3,168	3,560	+132	+4.3
34	3,300	3,300	3,752	0	0.0
35	2,640	2,530	2,660	—110	—4.1
36	2,596	2,596	2,587	0	0.0
37	4,180	4,180	4,125	0	0.0
38	4,114	4,202	4,400	+ 88	+2.0
39	5,192	5,148	4,850	— 44	—0.8
40	4,466	4,532	4,075	+ 66	+1.4
41	4,378	4,466	4,575	+ 88	+2.0
42	3,608	3,564	3,900	— 44	—1.2
43	3,652	3,608	4,027	— 44	—1.2
44	3,564	3,608	3,850	+ 44	+1.2
45	3,850	3,630	4,200	—220	—5.7
46	3,674	3,696	4,225	+ 22	+0.6
47	4,114	4,114	3,645	0	0.0
48	4,884	4,864	4,150	— 20	—0.4
49	2,640	2,728	2,880	+ 88	+3.3
50	3,542	3,520	3,500	— 22	—0.6
51	3,190	3,256	3,500	+ 66	+1.7
52	2,618	2,574	2,700	— 44	—1.6
53	5,148	5,082	4,325	— 66	—1.2
54	3,542	3,542	3,220	0	0.0
55	3,234	3,014	2,813	—220	—6.8
56	2,970	3,036	2,940	+ 66	+2.2
57	2,244	2,420	2,540	+176	+7.8
58	3,894	3,982	4,550	+ 88	+2.2
59	3,454	3,564	2,880	+110	+3.1
60	4,180	4,048	3,850	—132	—3.1
61	2,772	2,838	3,080	+ 66	+2.3
62	2,530	2,376	2,880	—154	—6.0
63	2,420	2,442	2,860	+ 22	+0.9
64	5,390	5,632	4,375	+242	+4.2
65	4,180	4,312	3,975	+132	+3.1
66	4,510	4,466	4,325	— 44	—0.9
67	3,652	3,960	4,275	+308	+8.4
68	5,325	5,475	4,500	+150	+2.8
69	3,718	3,718	4,625	0	6.0
70	2,618	2,662	3,160	+ 44	+1.5
71	4,904	3,696	5,250	—308	—7.6
72	3,820	3,520	4,675	—300	—7.7
73	2,046	2,222	2,520	+176	+8.6
74	3,674	3,630	3,000	— 44	—1.1
75	2,948	3,146	3,900	+198	+6.7
76	5,192	5,324	4,175	+132	+2.5
77	4,774	5,038	4,000	+264	+5.5
78	4,994	4,906	3,915	— 88	—1.8
79	2,838	2,860	3,575	+ 22	+0.7

TABLE 1.—*Normal Cases—(Continued)*

Case	Vital Capacity Before Dry Air, Cc.	Vital Capacity After Dry Air, Cc.	Expected Vital Capacity, Cc.	Gain or Loss in Cc.	Gain or Loss in Percentage
80	4,488	4,334	4,150	—154	—3.4
81	2,904	2,904	3,475	0	0.0
82	5,390	5,148	4,100	—242	—4.4
83	3,454	3,432	3,500	— 22	—0.6
84	3,498	3,256	3,800	—242	—6.9
85	3,542	3,564	3,180	+ 22	+0.6
86	5,016	5,126	4,500	+110	+2.1
87	2,926	2,882	3,200	— 44	—1.5
88	3,168	3,168	2,760	0	0.0
89	3,498	3,300	2,980	—198	—5.6
90	3,938	3,872	4,300	— 66	—1.6
91	4,312	4,488	4,250	+176	+4.0
92	5,588	5,566	4,300	— 22	—0.4
93	3,256	3,234	3,892	— 22	—0.5
94	3,630	3,848	3,850	+218	+3.5
95	4,400	4,400	4,400	0	0.0
96	3,476	3,410	3,300	— 66	—1.2
97	3,696	3,742	3,320	—154	—4.1
98	3,674	3,696	3,397	+ 22	+0.5
99	4,620	4,554	4,275	— 66	—1.0
100	5,082	5,390	4,250	+308	+6.6

that of the diaphragm, to produce medial movement. In a normal person the costal margin moves laterad because the balance of power is in favor of the intercostal muscles. This ascendency of power is due to the mechanical disadvantage of the diaphragm which, because of its dome, exerts its traction in a curved rather than in a straight line between its points of origin in the central tendon and insertion at the costal margin. Anything which will depress the diaphragm, making the line of traction more nearly a straight line, will decrease the disadvantage and finally may give ascendency of power to the diaphragm. Under such circumstances, the costal margin will move laterad to a lesser degree, become stationary or move mediad according to the degree of depression of the diaphragm. It should be kept in mind that enlargement of the heart or a pericardial effusion depresses only that part of the diaphragm attached to the costal margin from the ensiform process to the seventh costal cartilage, and pleural effusion or emphysema that part from the seventh costal cartilage laterally. Therefore, enlargement of the heart or pericardial sac limits the outward movement of the medial portion of the costal margin during inspiration, and an emphysematous lung or pleural effusion limits the movement of the lateral portion of the costal margin. A markedly emphysematous lung may affect also the entire costal margin. It is important to understand this conception of the effect of emphysema on the costal margins because otherwise a case like the following could not be explained. A patient with bronchiolar hypertonus and emphysema showed the entire extent of both costal margins moving mediad with inspiration, a tympanitic percussion note throughout the chest, low lung bases with no excursion during respiration, and a marked diminution of vital capacity. A dose of 1 cc. of epinephrine hydro-

chloride subcutaneously gave an increase of vital capacity and good outward excursion of the costal margins during inspiration, but the lung bases remained at the same level and continued to show no excursion. This observation can be explained only on the basis of a marked emphysema of both lungs which depressed the diaphragm and resulted in mediad movement of the costal margins before the injection of epinephrine hydrochloride, and a marginal emphysema of the lung bases which persisted after the injection of the drug, but which was not sufficient to depress the diaphragm.

With this concept understood, the significance of changes in the movement of the costal margins after breathing dry air is obvious. If, as was found in many cases of emphysema, the costal margins were moving mediad before breathing dry air and laterad subsequently, only one conclusion could be reached, namely, that a diminution of lung volume had occurred as a result of the dry air. This diminution of emphysema could have been accomplished only by a lessening of bronchial moisture which had caused bronchial stenosis and thereby produced localized or generalized emphysema.

It is not conceivable that bronchial stenosis due to any other factor than moisture could be modified by dry air. Furthermore, it is equally inconceivable that vital capacity reduced by encroachment on, or limitation of, movement of the lungs could increase as a result of dry air. In myocardial failure with edema in the bronchial tree, however, there is abundant opportunity for some or all of the bronchi to become partially or completely stenosed, with a resultant emphysema. This is the type of case that will respond to dry air with an increase of vital capacity, a decrease of emphysema, an increased motility of the lung and chest wall and subjective improvement.

There are cases of mild cardiac decompensation which show a decreased vital capacity, but no moisture in the bronchi. Von Basch [3] in 1889 advanced the idea that increase of arterial pulmonary pressure caused a distention of the alveolar capillaries, thus producing a stiffening (Lungenstarheit) which interfered with expansion and retraction of the lungs. Siebeck [4] reached a similar conclusion. Recent work of Drinker, Peabody and Blumgart [5] gives credit to this theory, but it is considered less important in reducing vital capacity than the "inward swelling" (Lungenschwelling of von Basch) of the capillaries, which tends to diminish alveolar space. Lundsgaart [6] attributes the initial loss of vital capacity to increase of residual air, that is, stiffening of the lung.

3. Von Basch, S.: Wood's Medical and Surgical Monographs, vol. 3, no. 1, 1889.

4. Siebeck R.: Arch. f. klin. Med. **100**:204, 1910.

5. Drinker, Peabody and Blumgart: J. Exper. Med. **35**:77 (Jan.) 1922.

6. Lundsgaart, C.: Determination and Interpretation of Changes in Lung Volumes in Certain Heart Lesions, J. A. M. A. **80**:163 (Jan. 20) 1923.

In the later stages of decompensation, however, he attributes it entirely to diminished air space. If a lung is rigid because of engorged capillaries and interstitial edema, or the air space is limited by the "inward swelling" of the capillaries, no change could be expected from breathing dry air. If in addition to the factors mentioned above, there was also bronchial edema, there would be an increase of vital capacity caused by dry air in proportion to the amount of resultant bronchial stenosis.

A few selected cases will be illustrative of the above discussion.

REPORT OF CASES

CASE 2.—L. C., aged 40, had a condition diagnosed as syphilitic aortitis, aortic insufficiency, aneurysm of the sinus of valsalva and myocardial insufficiency.

The costal margins were moving mediad before the experiment, and there were many râles in the lungs. The vital capacity was 2,134 cc. before breathing dry air and 2,376 cc. afterward, a gain of 242 cc., or 11.3 per cent. The expected vital capacity was 4,323 cc. The patient experienced considerable relief, and the costal margins were now moving laterad. There was no change in the number of râles.

In this case necropsy showed the aneurysm to be very small and the aorta not greatly dilated; therefore, neither could have produced bronchial stenosis. The only remaining factor for the production of stenosis and the resulting emphysema was moisture in the bronchial tree due to myocardial insufficiency. Breathing dry air decreased lung volume, as shown by the movement of the costal margins. An increase of vital capacity was additional proof of decreased emphysema. The vital capacity did not rise to normal because it was partly inhibited by lung rigidity caused by engorged capillaries and interstitial edema.

CASE 18.—E. McT., aged 54, had a condition diagnosed as myocardial insufficiency, generalized arteriosclerosis, chronic myocarditis and chronic nephritis.

Examination showed crepitant and bronchial râles throughout the lower part of the chest. There was a slight amount of fluid in the left pleural cavity. The lateral portion of the left costal margin was stationary, but the medial portions and right lateral portion were moving laterad with inspiration. The expected vital capacity was 4,072 cc., but the actual only 1,452 cc. After the patient had breathed dry air for five minutes, the vital capacity was 1,496 cc. After a further nine minute period, it was 1,716 cc., a gain of 264 cc., or 18.2 per cent over the patient's vital capacity before breathing dry air. Breathing dry air was continued for six minutes more with a resultant vital capacity of 1,804 cc., a further gain of 88 cc., or 5.1 per cent. Thus there was a total gain of 352 cc., or 24.2 per cent. Examination at this time showed fewer of both types of râles, particularly the bronchial. The left lateral costal margin was now moving laterad freely with inspiration. The patient felt better and could breathe easier because he said, "There is less tightness in my chest."

On a later date, examination showed no râles in the lungs, good lateral excursion of the costal margins with inspiration and no respiratory difficulty. The vital capacity was now 3,630 cc., and dry air gave no increase.

In this case, nephritis could have been the cause of a reduced vital capacity, but it was the opinion that myocardial insufficiency was the most important factor in the production of bronchiolar moisture. There was no condition other than moisture to produce bronchiolar stenosis. The lateral portion of the left costal margin could have been limited in its outward excursion during inspiration by fluid in the pleural cavity on that side, but was due rather to localized emphysema of the left lower lobe, which was caused to disappear by breathing dry air. Here again, an increased vital capacity was a proof of the foregoing observations. The later experiment, when no increase of vital capacity was obtained, was performed at a time when emphysema was not present.

CASE 25.—M. S., aged 43, had a condition diagnosed as myomalacia cordis, coronary thrombosis and myocardial insufficiency.

On the day of the experiment there was an undeterminable amount of fluid in both pleural cavities with emphysema of both upper lobes of the lungs and a few crepitant and bronchial râles. Both costal margins were moving mediad in their entire extent. The expected vital capacity was 4,825 cc., and the actual only 1,474 cc. After breathing dry air, it rose to 1,672 cc., a gain of 198 cc. or 13.4 per cent. The lateral portion of the right costal margin was now moving laterad. There was no change in the râles.

In this case there was nothing to account for bronchial moisture and stenosis except myocardial insufficiency. The diaphragm was depressed on both sides causing a medial movement of the costal margins. After breathing dry air, emphysema of the right lower lobe was decreased, and the costal margin on that side moved laterad with inspiration. Thus there was a combination of fluid and emphysema on the right side and fluid alone in the lower part of the left side of the chest. Dry air could not modify the decreased vital capacity due to the pleural effusion, but had an appreciable effect by decreasing the emphysema present in the right lower lobe.

CASE 38.—T. T., aged 49, had a condition diagnosed as auricular fibrillation with myocardial insufficiency, asthma and chronic emphysema.

The vital capacity before and after breathing dry air was 2,420 cc., and 2,706 cc., a gain of 286 cc., or 11.4 per cent. Before the experiment the costal margins were moving mediad throughout their entire extent, and there were many bronchial râles. After the patient had breathed dry air, there were fewer râles, and both costal margins were moving strongly laterad with inspiration.

In this case a decrease of vital capacity could have been due to myocardial insufficiency, bronchiolar hypertonus or atrophic emphysema. Since the volume of the lung was changed markedly by breathing dry air as shown by costal margin movement, a part of the emphysema must have been due to partial stenosis of the bronchi by moisture.

CASE 42.—C. B., aged 54, had a condition diagnosed as exophthalmic goiter, chronic myocarditis with myocardial insufficiency, auricular fibrillation and arteriosclerosis with hypertension and emphysema.

On the day of the experiment the lung bases were at the level of the twelfth rib in the midscapular lines. The medial portions of the costal margins were moving mediad and the lateral portions slightly laterad with inspiration. There were crepitant râles at the lung bases posteriorly. The vital capacity was 3,278 cc., and was not changed by quiet breathing of dry air. After a five minute period of deep breathing, however, it was elevated to 3,564 cc., a gain of 286 cc., or 8.7 per cent. The expected vital capacity was 3,915 cc. After the last part of the experiment, the râles were fewer; the costal margins were moving laterad throughout their entire extent with inspiration, and the lung bases were elevated 2 cm.

In this case moisture in the bronchi due to myocardial insufficiency caused emphysema. This in turn resulted in a decreased vital capacity and increase of lung volume. Breathing dry air decreased the lung volume, as shown by the position of the bases and the excursion of the costal margins.

Table 2 shows the results obtained in a series of cases, similar to those cited above, in which myocardial insufficiency was the cause of pulmonary edema, increased volume of the lung and diminished vital capacity. There was an average increase of 190 cc., or 11.4 per cent in vital capacity as a result of breathing dry air. The greatest increase was 484 cc., or 50.8 per cent, and the lowest figure was a decrease of 88 cc., or 8.3 per cent. Eighty-two per cent of the determinations showed an increase from 110 to 484 cc., 7 per cent less than 100 cc., and 11 per cent a decrease of less than 100 cc.

These results are to be contrasted with those of table 1. The conclusion seems warranted that breathing dry air extracted sufficient moisture from the bronchial tree to decrease the resultant emphysema. That emphysema was present could not be doubted when the movement of the costal margins before and after breathing dry aid was observed. Emphysema, therefore, was one of the factors in the reduction of vital capacity, which was increased when the emphysema was decreased by extraction of moisture from the bronchi.

The foregoing results and conclusion are applicable only to patients who have emphysema caused by excessive moisture in the bronchial tree. In cardiac cases, with no signs of myocardial insufficiency except a lowered vital capacity, dry air should, theoretically, give no increase, and experimentally it does not. The decreased vital capacity in such cases is due to lung rigidity from engorged capillaries and interstitial edema. Therefore, since there is no excess of moisture in the bronchi, dry air can be of no value. Table 3 shows results in such cases. The average increase of vital capacity was 35 cc., or 1.3 per cent.

TABLE 2.—*Decompensated Cardiac Cases*

Case	Gain or Loss of Vital Capacity After Dry Air, Cc.	Gain or Loss in Percentage	Case	Gain or Loss of Vital Capacity After Dry Air, Cc.	Gain or Loss in Percentage
1	+110	+ 7.2	25	+198	+13.4
2	+242	+11.3	27	+110	+11.9
3	+330	+14.0	29	+154	+25.0
4	+ 22	+ 1.1	30	— 44	— 4.0
8	+242	+12.1	32	+154	+ 5.6
	— 44	— 2.7	36	+264	+ 7.7
9	+220	+12.8	38	+286	+11.4
17	+ 66	+ 3.0	39	+198	+12.0
	+176	+ 8.4	41	+220	+11.4
18	+352	+24.2	42	+286	+ 8.7
19	+264	+23.1	43	+176	+ 4.5
20	— 88	— 8.3	49	+484	+52.3
21	+378	+13.7		+198	+20.4
24	+196	+ 7.2			

Several illustrative cases are given below.

CASE 6.—F. M., aged 43, had a condition diagnosed as: acute fibrinous pericarditis, acute myocarditis and auricular fibrillation.

On the day of the experiment there were no abnormal physical signs except an occasional râle at the lung bases. The expected vital capacity was 3,800 cc. Before and after the patient had breathed dry air, the vital capacity was 2,838 cc., and 2,882 cc., a gain of 44 cc., or 1.5 per cent.

The actual vital capacity in this case was about 1,000 cc. less than the expected capacity. There was little free moisture in the bronchial tree and no emphysema, as was shown by the normal excursion of the costal margins. Lung rigidity due to cardiac stasis and not to emphysema, therefore, was the cause of a decreased vital capacity. Since dry air could not affect the rigidity of the lung, it could likewise not affect vital capacity.

CASE 11.—L. McL., aged 28, had a condition diagnosed as mitral stenosis and insufficiency.

There was a good state of cardiac sufficiency with the exception of a vital capacity of 1,870 cc., as contrasted with an expected vital capacity of 2,960 cc. After the patient had breathed dry air, the vital capacity was 1,848 cc., a loss of 22 cc., or 1 per cent.

The reduced vital capacity in this case was due to the same causative factor mentioned in case 6.

There is another type of case in which dry air should produce no change in vital capacity, namely, atrophic emphysema, and this probably accounts for failure to obtain an increase in certain cases of asthma of long duration. There are patients with asthma, however, who do respond with an increase of vital capacity, and who show objective and subjective change after dry air. Which patient will respond in this manner, and which will not is a matter of conjecture, but this makes the experiment of clinical value because it makes possible the classification of patients.

Those who respond favorably to a short test with dry air probably would find a climate with a lower relative humidity much more comfortable and less conducive to acute attacks. If all cases of asthma were due to free moisture in the bronchi, dry air would be of advantage

TABLE 3.—*Compensated Cardiac Cases*

Case	Gain or Loss of Vital Capacity After Dry Air, Cc.	Gain or Loss in Percentage	Case	Gain or Loss of Vital Capacity After Dry Air, Cc.	Gain or Loss in Percentage
[illegible]	0	0.0	15	+ 22	+0.8
[illegible]	+44	+1.5	16	+146	+5.9
[illegible]	+64	+1.0	18	0	0.0
[illegible]	+22	+0.8	28	+ 66	+1.6
[illegible]	—22	—1.0	41	+ 44	+1.5
[illegible]	0	0.0	46	0	0.0
[illegible]	+66	+5.0	47	+ 44	+1.3
[illegible]	+22	+0.9			

to the entire group. However, there are cases with little moisture, as shown by few râles and minimal expectoration. The mechanism of bronchial obstruction in such cases is not clearly understood. It may be due to hypertonus of the bronchi according to the common conception or, according to a newer idea, to hives of the bronchial mucosa similar to those seen in the skin in protein sensitization.

The recent unpublished work of Hoover and Beams (Lakeside Hospital) proves that emphysema, as produced in guinea-pigs during anaphylaxis, is not caused by bronchiolar hypertonus, but by edema of the mucosa which produces wheals not unlike those seen in urticaria of the skin. This condition results in bronchial stenosis and emphysema.

Regardless of condition, whether it be hypertonus or hives, the fact remains that the obstruction in the bronchus is not free moisture and should not in any way be affected by breathing dry air. If there is a combination of both, dry air might be of some value. Accordingly, a number of patients with asthma were tested with dry air before and after the giving of epinephrine hydrochloride.

Cases 49, 50, 52 and 54 (table 4) amplify the foregoing discussion.

TABLE 4.—*Effect of Dry Air Before and After the Use of Epinephrine Hydrochloride in Asthma and Emphysema*

Case	Gain or Loss of Vital Capacity Before Epinephrine Hydrochloride, Cc.	Gain or Loss in Percentage	Gain or Loss of Vital Capacity Due to Epinephrine Hydrochloride, Cc.	Percentage	Gain or Loss of Vital Capacity After Epinephrine Hydrochloride, Cc.	Gain or Loss in Percentage
1	0	0.0	+ 110	+ 7.7	+110	+ 7.2
13	0	0.0	+ 198	+ 12.0	+ 22	+ 1.2
26	+44	+ 1.5	.....	.....	.....	.....
40	—110	— 6.0	.....	.....	.....	.....
44	+178	+13.1	.....	.....	.....	.....
49	+286	+31.0	0	0.0	+198	+18.0
50	0	0.0	.....	.....	.....	.....
51	0	0.0	.....	.....	.....	.....
52	— 44	— 1.6	+1,076	+ 39.1	+462	+12.5
53	+ 44	+ 4.1	.....	.....	.....	.....
54	+260	+21.1	+1,588	+106.4	+418	+13.6
	.....	.....	.....	.....	+286	+ 8.3
55	.....	.....	+ 220	+ 10.8	+154	+ 4.7
56	0	0.0	.....	.....	.....	.....

Table 5 shows the results obtained in several cases of pulmonary infiltration, but the results are too few for comment. It seems likely that further work will show an increase of vital capacity in resolving lobar pneumonia or a bronchopneumonia with considerable bronchial moisture.

TABLE 5.—*Pulmonary and Pleural Conditions*

Case	Gain or Loss of Vital Capacity After Dry Air, Cc.	Gain or Loss in Percentage	Condition
26	+308	+12.8	Lobar pneumonia
31	0	0.0	Bronchitis
33	+ 44	+ 1.3	Lobar pneumonia
34	+110	+ 4.3	Pleurisy with effusion
35	+198	+ 8.8	Bronchopneumonia
37	— 44	— 1.8	Lung abscess
45	+176	+ 4.8	Pleurisy with pulmonary infiltration
48	+ 22	+ 0.9	Lobar pneumonia

ASTHMATIC CASES

CASE 49.—J. K., aged 48, had a condition diagnosed as chronic emphysema, chronic bronchitis, chronic myocarditis and myocardial insufficiency.

This patient entered the hospital because of shortness of breath, edema of the legs, swollen abdomen and palpitation, all of which were of two weeks' duration. Asthma had been present for twelve years. On the day of the experiment, the examination showed a marked degree of cyanosis, the heart enlarged in all diameters, and poor motility of the lungs, as shown by diminished undulation and the mediad movement of the entire extent of both costal margins. The percussion note was tympanitic throughout the chest, and there were many musical and bronchial râles.

The expected vital capacity was 4,225 and the actual 924. After the patient had breathed dry air for five minutes, the vital capacity was 1,210—an increase of 286 cc., or 31 per cent. The costal margins were now moving laterad throughout their entire extent, but there was no change in the number or character of the râles. The patient felt distinctly better. Ten minutes after

breathing the dry air, the patient's vital capacity was 1,122 cc., and the left lateral costal margin was stationary. After the administration of 7 mm. of epinephrine hydrochloride, the vital capacity was 1,122 cc., and thirty minutes later it was 1,100 cc.—there being no effect objectively or subjectively caused by the drug. Dry air was again used for ten minutes, and the vital capacity rose to 1,298 cc., an increase of 198 cc., or 18 per cent. Both costal margins were moving vigorously in the laterad direction, and there was further subjective improvement. This case showed a total increase of 484 cc., or 52.3 per cent, due entirely, therefore, to the breathing of dry air. A subsequent observation on the same patient showed the following: The vital capacity before and after the breathing of dry air was 924 and 1,034 cc., respectively, an increase of 110 cc., or 11.9 per cent. Dry air was now continued for another ten minute period which resulted in an elevation to 1,122 cc.—a further increase of 88 cc., or 8.5 per cent. Thus there was a total increase in this instance of 198 cc., or 20.4 per cent. The costal margins which had been moving mediad before the experiment were now moving laterad.

In this case decreased vital capacity could have been due to myocardial insufficiency, bronchiolar hypertonus, bronchiolar edema, atrophic emphysema or a combination of these conditions.

Before the patient had breathed dry air, the costal margins were moving mediad with inspiration, indicating in the light of other physical observations, a low position of the diaphragm due to emphysema. After the breathing of dry air, both costal margins moved laterad with inspiration, indicating a lessening of the emphysema. An increased vital capacity also resulted. The conclusion can be drawn, therefore, that one factor causing a decrease of vital capacity was moisture in the bronchial tree which resulted in emphysema. The vital capacity was not affected to a greater degree because of atrophic emphysematous changes and rigidity from cardiac decompensation. After a ten minute interval, the vital capacity had dropped about 100 cc., and, what was more striking, the left lateral costal margin was now stationary on inspiration. The latter observation indicated an increase of emphysema of the left lower lobe as the result of a recurrence of moisture in that part of the bronchial tree. At this time, epinephrine hydrochloride gave no change of physical signs or vital capacity; therefore the emphysema was not due to bronchial hypertonus. The breathing of dry air then caused the left lateral portion of the costal margin to move laterad with inspiration. At a later date, the experiment was repeated with similar results.

Thus it may be concluded from this case that moisture in the bronchial tree caused emphysema and decreased vital capacity. Bronchiolar hypertonus contributed nothing to the decrease of vital capacity, but cardiac stasis and possibly atrophic emphysema contributed to a great degree. These factors could not be modified by dry air; therefore there was not a greater increase of vital capacity.

Case 50.—P. B., aged 42, had a condition diagnosed as allergic asthma.

Seven months prior to admission to the hospital, the patient had had an attack of what appeared to be hay-fever which later developed into a typical asthma. There had been several severe attacks since the onset. The expected vital capacity was 3,875 cc., and the actual 3,080 cc. At this time the patient was not having paroxysms, and there were no physical signs except a few musical râles in the chest. After the patient had breathed dry air for five minutes, the vital capacity remained the same, and there was no change as to râles or subjective improvement. A later determination during a paroxysm showed the vital capacity to be 1,800 cc. before and after a ten minute period of breathing dry air. There were no more râles at this time, but the dry air

produced no change, and there was also no subjective improvement. A still later determination gave 1,562 cc. before and after dry air, and this time there was a profusion of bronchial râles, restraint of lateral portion of the costal margin and a depression of the lung bases. The experiment accentuated unpleasant subjective symptoms. The administering of epinephrine hydrochloride gave almost instantaneous relief, but unfortunately the vital capacity was not secured at this time.

In this case bronchial obstruction was due to hypertonus or hives and not to moisture. As was to be expected, dry air gave no relief whereas epinephrine hydrochloride markedly changed physical signs and vital capacity.

CASE 52.—J. K., aged 50, had a condition diagnosed as asthma.

There were only a few musical râles in the lungs, and the motility of the chest was good at the time of the experiment. The expected vital capacity was 4,432 cc., and the actual 2,750 cc. After the patient had breathed dry air for five minutes, the vital capacity was 2,706 cc., a loss of 44 cc., or 1.6 per cent. After a further five minute period, it was 2,640 cc., a further loss of 66 cc., or 3.5 per cent. After the administration of 10 mm. of epinephrine hydrochloride, the vital capacity rose to 3,690 cc., a gain of 1,056 cc., or 39.1 per cent. After full effect from the epinephrine hydrochloride, the vital activity remained at 3,696 cc.; dry air was now breathed for five minutes, and the vital capacity rose to 4,158 cc., a further gain of 462 cc., or 12.5 per cent.

The reduction of vital capacity in this case was due to bronchial obstruction partly from moisture and partly from hypertonus. Dry air caused no change before epinephrine hydrochloride was injected, and it may be hypothecated that regional hypertonus prevented the dry air from reaching the bronchioles in which there was moisture. After full effect from the epinephrine hydrochloride, however, dry air gave a further gain of vital capacity. The additional hypothesis may be stated that when the regional hypertonus was removed by epinephrine hydrochloride, dry air penetrated to the bronchioles and removed moisture which still remained a partial cause of obstruction.

CASE 54.—F. F., aged 53, had a condition diagnosed as chronic bronchitis with emphysema and asthma.

Examination showed the costal margins to be moving mediad throughout their entire extent. The lung bases were at the twelfth rib in the midscapular line, and there were musical râles throughout the chest. The expected vital capacity was 4,275 cc. and the actual only 1,232. After the patient had breathed dry air for five minutes, the vital capacity was 1,492 cc., a gain of 260 cc., or 21.1 per cent. There was considerable subjective but no objective change in the patient's condition. Ten minims of epinephrine hydrochloride was now given and six and one-half minutes later the vital capacity was 3,080 cc., a gain of 1,588 cc., or 106.4 per cent. There was no further increase six and one-half minutes later. The costal margins were now moving laterad throughout. The right base was elevated 3 cm. and the left, 5 cm. All the râles with the exception of a few crepitant ones at the bases, had disappeared. There was, of course, marked subjective improvement. Dry air was now instituted for five minutes, and the vital capacity rose further to 3,498 cc., a gain of 418 cc., or 13.6 per cent. There were no further changes in the physical signs, but the patient felt better and resented the discontinuing of breathing dry air.

This case presents bronchial obstruction from a combination of hypertonus and moisture. Dry air increased the vital capacity by extracting a part of the bronchial moisture; epinephrine hydrochloride increased it markedly by relieving hypertonus, after which dry air was still further effective by penetrating bronchi in which moisture still produced a stenotic affect.

SUMMARY

1. An experimental method is described for testing the effect, on vital capacity, of breathing dry air.

2. One hundred patients, normal as to heart and lungs, were tested. The average increase of vital capacity in these cases was 12.5 cc. or 0.3 per cent.

3. A number of patients with cardiac decompensation were tested; there was an average increase of 190 cc., or 11.4 per cent.

4. In patients with cardiac compensation there was an average increase of only 35 cc., or 1.3 per cent.

5. Patients with asthma varied in their response. Several responded with an increase before and after the injection of epinephrine hydrochloride. Others responded with an increase due to dry air and none to epinephrine hydrochloride; the response in others was just the reverse.

CONCLUSIONS

The conclusion seems justified that breathing dry air extracts enough of the moisture to increase temporarily the vital capacity in the majority of patients with bronchiolar edema, decrease the lung volume and number of râles and produce a sense of subjective relief. However, if the vital capacity is reduced because of bronchial obstruction other than moisture, interstitial pulmonary edema or a rigid lung due to stasis, breathing dry air causes no change. The procedure may also be used to differentiate between those patients with asthma whose bronchial obstruction is due chiefly to moisture and not to hypertonus or hives and thus will be selective of cases in which the patients will improve, in all probability, in a dryer climate.

INTRAVENOUS INJECTION OF OUABAIN IN MAN*

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During the past five years, in the third medical (New York University) division of Bellevue Hospital, we have been making controlled observations on the preparations, dosage, absorption and evidences of disappearance of the digitalis bodies in patients suffering from organic heart disease. Studies have been made, in conjunction with Eggleston [1] and the Cornell medical division, on the absorption of digitalis when given by mouth, on the dosage and absorption of digitalis rectally administered and on the absorption and dosage of various preparations given hypodermically. We have found that absorption from the gastro-intestinal tract is so rapid and uniform, and when given in maximum dosage, complete digitalization takes place so promptly (within six to eight hours), that we have felt little practical need for giving the drug intravenously.

However, every physician is confronted from time to time with patients who, because of persistent vomiting due to the passive congestion caused by heart failure, are unable to retain digitalis given by mouth. Such patients usually can be given digitalis by rectum, but we have had experience with a few patients who were unable to retain the drug when it was given by this method. These patients are in need of digitalization, and one must resort to hypodermic medication. If the intravenous method is safe, it would seem to be the method of choice because of its rapidity of action, and because there is no after-pain as is the case with subcutaneous or intramuscular injections.

Furthermore, it occurred to us that if the action of intravenous medication is as rapid as has been described, it might be possible to give fractional doses at such short intervals that total digitalization could be produced rapidly. A comparison might be made, as was done by Eggleston [2] (with digitalis by mouth), as to the dose required in relation to sex, age, cardiac condition and body weight. By the intravenous method these results should be more accurate as the variables of absorp-

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* From the Third Medical (New York University) Division and Adult Cardiac Clinic of Bellevue Hospital.
* Read before the Section of Medicine, New York Academy of Medicine, April, 1926.

1. Eggleston, C., and Wyckoff, J.: The Absorption of Digitalis in Man, Arch. Int. Med. **30**:133 (Aug.) 1922.
2. Eggleston, C.: Digitalis Dosage, Arch. Int. Med. **16**:1 (July) 1915.

tion and elimination are greatly diminished. The end reaction also, namely, the point of complete therapeutic digitalization, should be more accurately determined, as it is possible to have the patient under continuous observation from the initial dose to the time of complete digitalization.

It was decided to use intravenously a preparation which was readily procurable and standard in its activity. Ouabain, which is amorphous strophanthin, otherwise known as strophanthin gamma, was the preparation decided on. Hatcher and Bailey [3] have shown it to be a standard preparation. Cohn and Levy [4] and others have described its activity on man. As in the case of other digitalis like intravenous preparations, there is considerable divergence of opinion, however, as to its dosage. Hatcher and Bailey state that no more than 0.5 mg. should be given in twenty-four hours. Cohn and Levy, on the other hand, have given twice that amount (1.1 mg.) in two hours. Levin and Cunningham's [5] experiments showed the margin between the minimum toxic dose and the minimum lethal dose to be 48 per cent. Levine, therefore, recommends that the drug be injected intravenously in small doses, 0.1 mg. every half hour, so that there will be no danger of giving an excess of more than 0.1 mg. of the minimum toxic dose; the sign of intoxication should be carefully watched for during the intervals between injection.

Cases of sudden death following the intravenous injection of all of the digitalis-like bodies have frequently been reported. Levine believes that such accidents may be avoided by the fractional method of dosage; particularly is this true if partial digitalization has been produced before the patients are given intravenous medication.

The reports of such cases of sudden death have made physicians wary as to the use of intravenous medication. In spite of this fact, Levine states that Vasquez and Luttenbacher have reported nearly 2,000 intravenous injections of ouabain without harm or fatality. On the other hand, Cohn and Levy,[4] giving ouabain at one hour intervals, the first dose being from 0.4 to 0.5 mg. and the second usually from 0.3 to 0.5 mg., found that ventricular premature contractions or ventricular paroxysmal tachycardia developed in 52 per cent of their patients with auricular fibrillation and in 12.5 per cent of the patients in whom there was regular sinus rhythm. When comparable doses of digitalis were given by mouth, only one-half that percentage of toxic effects was noted.

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3. Hatcher, R. A., and Bailey, H. C.: The Clinical Use of Strophanthus, J. A. M. A. **55**:1697 (Nov.) 1910.

4. Cohn, A., and Levy, R.: A Comparison of the Action in Patients of G-Strophanthin and Digitalis, Proc. Soc. Exper. Biol. and Med. **17**:81, 1919-1920.

5. Levine, S. A., and Cunningham, T. D.,: The Margin of Safety of Intravenous Digitalis in Cats, Arch. Int. Med. **26**:293 (Sept.) 1920.

Cohn and Levy [4] state that it is rare for the dosage of ouabain used by them on patients with auricular fibrillation to decrease the rate of the ventricle for more than five days.

EFFECT OF OUABAIN ON PATIENTS WITH ORGANIC HEART DISEASE

As in a cardiac service in which more than 300 patients with various degrees of heart failure are admitted every year, patients are occasionally seen who would be benefited by extremely rapid digitalization if it is safe, it was decided to make a study of the intravenous dosage of ouabain necessary to produce therapeutic effects, its action time and the time of the persistence of the action.

For the purpose of studying the rate of absorption and total dose needed, patients having organic heart disease with auricular fibrillation were selected. These patients were put at rest in bed on a limited fluid intake and a uniform diet. Daily observations were made as to the ventricular rate, pulse rate, weight, water intake and urine output. The patients were observed in this way during a control period of from five to ten days. On the day on which ouabain was to be administered, observations of ventricular and pulse rates were made every five minutes (fig. 1), previous to the first injections by about one hour. At the end of that time the initial dose of ouabain was administered intravenously, and the drug was administered every half hour until a full therapeutic effect was obtained.

The first ten patients were given 0.1 mg. every half hour; after that an initial dosage of 0.5 mg. was usually given, because we had determined that all adult patients needed a larger dose. In these cases this large initial dose was followed by smaller doses, usually 0.1 mg. every half hour.

A beginning effect was considered to have taken place when an injection was followed by a definite ventricular slowing which persisted. Full therapeutic effect was considered to have been obtained when the ventricular rate was slowed to 80 or below with obliteration of the pulse deficit.

No patients who had received digitalis within two weeks were given ouabain.

The preparation of ouabain used was that put up by Lily and Co. in ampules containing 0.5 mg. in 2 cc. of solution; 0.1 mg. of this preparation equals one cat unit.

In all, 28 patients with auricular fibrillation, three with regular sinus rhythm and one with auricular flutter received 248 injections. Seven of these patients had a high temperature at the time they were examined. In analyzing our results of dosage, the patients with high temperatures have been studied separately from those with normal temperatures.

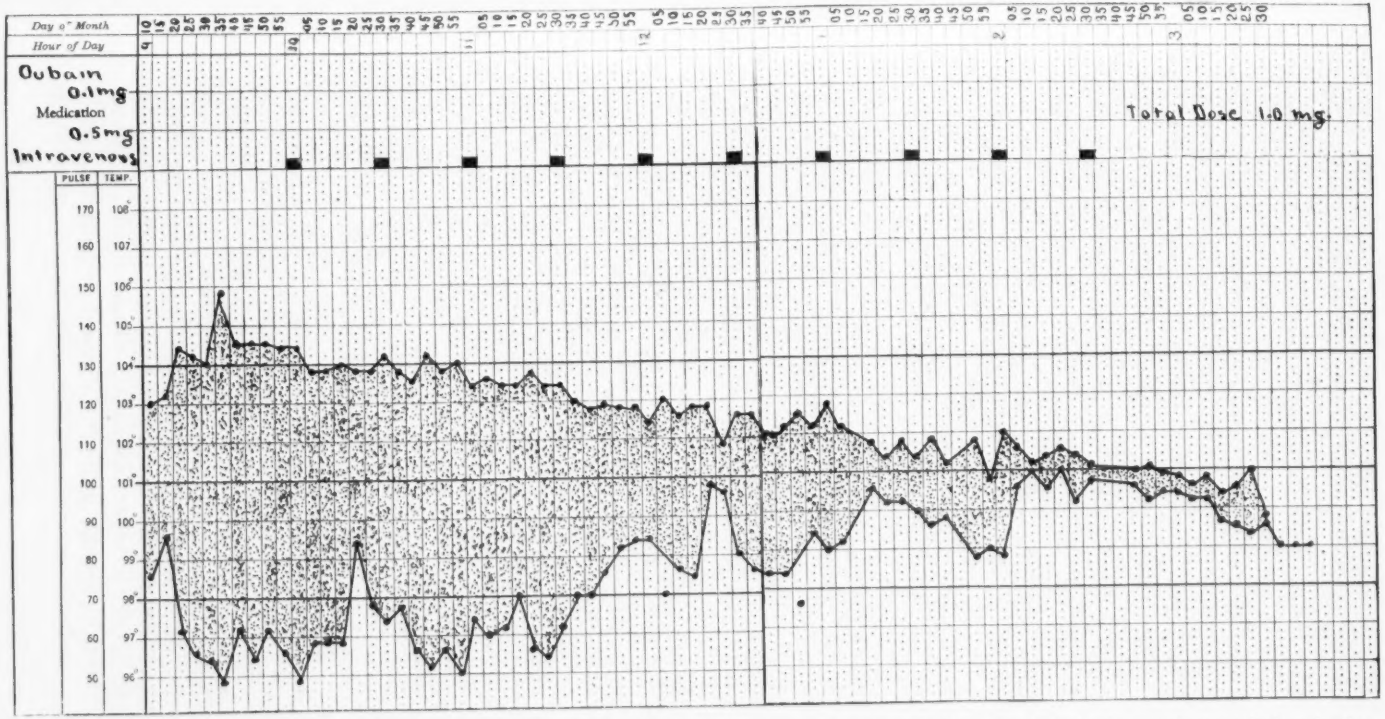

Chart 1 (Patient M. C.).—Observations made on ventricular and pulse rates on the day of injection, both during control period and after injection. The diagnosis was acute rheumatic fever, enlarged heart mitral stenosis and insufficiency and auricular fibrillation.

Table 1 shows the rapidity of action of ouabain given intravenously in auricular fibrillation. It will be seen that about one-half of the injections were followed by a beginning effect within five minutes, and that all except four which showed any effect did so within fifteen minutes.

It was thought that there might be some relation between the size of the dose and the rapidity of action. Observations are arranged in

TABLE 1.—*Rapidity of Action of Ouabain Given Intravenously in Auricular Fibrillation*

Total number of injections given	248
No effect noted (dose in all 0.25 mg. or less)	85
Effect noted in	163

Minutes After Injection Effect First Noted	Number of Cases
5	121
10	33
15	15
20	3
25	1

TABLE 2.—*Relation of Size of Dose of Ouabain to the Rapidity of Action*

Size of dose in Mg.	Total Number of Experiments	Number of Experiments Showing Action	Number of Experiments Showing No Action	Minutes After Injection First Action Noticed (Average)	Minutes After Injection Greatest Action Noticed (Average)
0.5	21	21	0	5	25
0.4	3	3	0	5	21
0.25	47	35	12	8.2	18
0.2	23	17	6	5.8	13
0.1	154	86	68	7.1	13.5

TABLE 3.—*Dosage in Mg. of Ouabain in Patients Without Elevation of Temperature*

Experiment Number	Mg. of Ouabain	Weight	Mg. Ouabain per Pound Body Weight	Experiment Number	Mg. of Ouabain	Weight	Mg. Ouabain per Pound Body Weight
1	0.8	149	0.0053	12	1.0	145	0.0051
2	1.0	149	0.0067	13	1.0	121	0.0082
3	1.1	149	0.0073	14	0.8	119	0.0067
4	1.7	187	0.0053	15	1.0	161	0.0062
5	0.7	210	0.008	16	0.85	160	0.0053
6	1.1	100	0.007	17	0.7	120	0.0058
7	1.1	123	0.0089	18	0.9	145	0.0062
8	0.95	126	0.0089	19	0.7	109	0.0064
9	0.95	148	0.0064	20	0.8	150	0.0063
10	1.0	133	0.0071	21	1.05	125	0.0084
11	0.75	133	0.0075				

Average dose per patient	0.95 mg.
Smallest dose per patient	0.7 mg. or 26.3% below average
Largest dose per patient	1.7 mg. or 78.9% above average
Average dose in mg. per pound of weight	0.0067 mg.
Smallest dose in mg. per pound of weight	0.0053 mg. or 20.9% below average
Largest dose in mg. per pound of weight	0.0089 mg. or 32.8% above average

table 2 so as to study such correlation. It will be seen that, as a rule, in patients receiving larger dosage, beginning action occurs more rapidly, but that it takes a longer time for full action of such a single dose.

Table 3 is arranged to show the dosage of ouabain in the patients without a rise in temperature. The weight noted in this table was the

weight of the patient free from edema. Regardless of body weight, it will be seen that the average dose per patient is 0.95 mg. The smallest dose which produced full therapeutic effect was 0.7 mg. or 26.3 per cent below the average dose. The largest dose needed by any patient was 1.7 mg. or 78.9 per cent above the average.

In terms of milligrams of ouabain per pound weight the average was 0.0067 mg. The smallest dose was 0.0053 mg. or 20.9 per cent below the average, and the largest dose was 0.0089 or 32.8 per cent above the average.

This would appear to bear out Eggleston's [2] statement that there is a distinct relationship between body weight and the amount of digitalis body necessary to produce a therapeutic effect.

Table 4 shows the same figures in seven patients having a rise in temperature. The average dosage both per patient and per pound body

TABLE 4.—*Dosage in Mg. of Ouabain in Patients with Elevation of Temperature*

Experiment Number	Mg. of Ouabain	Weight	Mg. Ouabain per Pound Body Weight	Experiment Number	Mg. of Ouabain	Weight	Mg. Ouabain per Pound Body Weight
1.....	1.5	138	0.011	5.....	1.0	90	0.011
2.....	1.55	150	0.010	6.....	1.55	139	0.011
3.....	1.25	149	0.0083	7.....	1.0	105	0.0095
4.....	1.0	94	0.0106				

Average dose per patient	1.23 mg.
Smallest dose per patient	1.0 mg. or 18.7% below average
Largest dose per patient	1.55 mg. or 9.7% above average
Average dose in mg. per pound of weight	0.01 mg.
Smallest dose in mg. per pound of weight	0.0083 mg. or 17.8% below average
Largest dose in mg. per pound of weight	0.011 mg. or 8.9% above average

weight was higher than in the patients with no elevation in temperature. The average dosage per patient was 1.23 mg., and the average dose in mg. ouabain per pound body weight was 0.01 mg. The smallest dose in this series which produced therapeutic effect was 1 mg. or 18.7 per cent below the average; the largest was 1.55 mg. or 9.7 per cent above the average.

The variations above and below the average in terms of milligrams of ouabain per pound body weight were 0.0083 mg. or 17.8 per cent below and 0.011 or 14.9 per cent above the average. In this small series the total dose per patient would seem to have no particular relationship to weight.

It was decided to determine whether it is possible to determine the rate of elimination or destruction of ouabain from the body. For this purpose after periods varying from two to nine days, ouabain was again administered intravenously, usually 0.1 mg. every half hour until the ventricular rate had been brought down to a point approximately the same as after the first full effect (fig. 2).

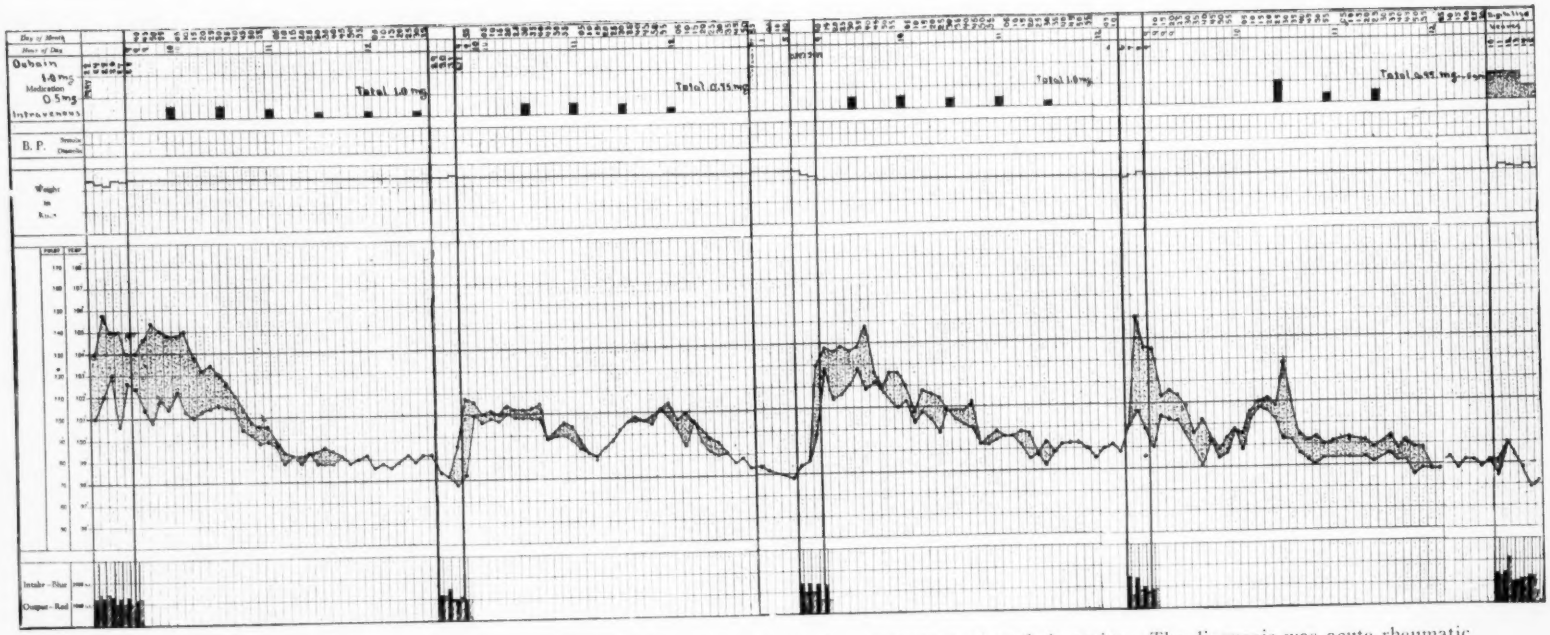

CHART 2 (Patient F. W.).—The type of observations made in order to determine persistence of ouabain action. The diagnosis was acute rheumatic fever, enlarged heart mitral stenosis and insufficiency and auricular fibrillation.

Table 5 shows the amount of ouabain needed to produce an effect similar to the effect of the initial dosage. This is shown both in milligrams of ouabain and in percentage of the initial dose. A study of this table shows a marked difference in the rate of elimination. It would seem that the drug is eliminated more rapidly during the first two or three days. There are other patients who seem to eliminate the drug more slowly, if this method can be relied on to show elimination.

TABLE 5.—*Studies in Elimination or Destruction of Ouabain*

Initial Dose, Mg.	Number of Days After Full Dosage Drug Resumed	Amount Needed to Produce Effect Similar to Effect of Initial Dosage, Mg.	Estimated Elimination Rate in 24 Hours, Mg.	Percentage of the Initial Dosage
1.55	2	0.95	0.47	61.3
1.0	2	1.0	0.5	100.0
1.7	2	1.0	0.5	58.8
1.7	2	1.0	0.5	58.8
0.8	3	0.35	0.117	43.5
0.8	3	0.55	0.183	68.5
0.95	3	0.6	0.2	63.2
1.0	4	1.0	0.25	100.0
1.0	4	1.0	0.25	100.0
1.0	4	1.0	0.25	100.0
0.95	4	0.95	0.24	100.0
1.0	4	0.5	0.125	50.0
1.0	4	0.5	0.125	50.0
0.7	4	0.5	0.125	71.4
1.55	4	1.35	0.34	87.7
0.95	5	0.85	0.17	89.4
1.0	5	0.7	0.14	70.0
0.95	6	1.0	0.16	105.0
1.0	7	0.7	0.1	70.0
1.0	9	0.85	0.093	85.0

TABLE 6.—*Persistence of Action of Ouabain After Full Therapeutic Effect*

Amount of Initial Dosage in Mg.	Duration of Persistence of Action in Days	Amount of Initial Dosage in Mg.	Duration of Persistence of Action in Days
0.65	1	0.7	4
0.5	1	0.7	4
		0.95	4
0.65	2	1.0	4
		1.55	4
0.8	3		
0.8	3	0.75	5
1.0	3		
1.05	3	0.7	9
1.05	3		

As we thought that the persistence of the action of ouabain might be an indication to the excretion of the drug, fifteen cases were studied after the initial dosage until all effects had disappeared. Table 6 shows the results of this study. While it again shows a wide variation, all except one of the patients showed that the action of the drug had disappeared at the end of five days. This is in accordance with the work of Cohn and Levy.[4]

Besides making these observations on the effect of ouabain on patients with auricular fibrillation, we treated with intravenous injections of ouabain three patients who had regular sinus rhythm; one patient was given a total of 0.8 mg. in three doses of 0.5 mg., 0.2 mg. and 0.1 mg. given one hour apart. A second patient was given 0.9 mg. in doses of 0.5 mg., 0.2 mg. and 0.2 mg. at one hour intervals. A third patient was given 0.5 mg. in five doses of 0.1 mg. each at intervals of one hour. All three of these patients showed marked clinical improvement. Hourly electrocardiograms were taken in these cases, but no definite increase in the P-R interval, and no marked or permanent T wave changes were noted. This also is in accordance with the observations of Cohn and Levy.[4]

One patient who had auricular flutter with 2:1 block received 1.25 mg. in four doses of 0.5, 0.25, 0.25 and 0.25 mg. at one hour intervals. This resulted in an increase of the 2:1 auricular ventricular block to 4:1 block, but there was practically no change in the rate of flutter, though the patient vomited. It was considered inadvisable to continue the administration of ouabain; all medication was stopped for six days, 2:1 block again returning. Digitalization was then produced by mouth, the patient receiving 13 cc. of a standardized tincture of digitalis or 0.1 of a cat unit per pound body weight in a single dose. The next day he was given 6 cc. more, making a total dosage of 19 cc. or 0.15 of a cat unit per pound body weight. The auricular flutter persisted with varying block. Two days later he was given 7 cc. of digitalis, making a total of 26 cc. or 0.2 cat unit per pound body weight; flutter persisted for forty-eight hours; then fibrillation suddenly set in without further digitalization.

In our series full therapeutic digitalization was produced fifty-two times in thirty-two different patients. One patient developed premature ventricular contractions; two patients developed vomiting. No other toxic symptoms were noted. There were no fatalities.

SUMMARY

Two hundred and forty-eight intravenous injections of ouabain were administered to thirty-two patients who had heart failure, without fatalities or harmful effects.

One hundred and sixty-three of these injections were followed by a definite cardiac effect. The initial effect was noted in from five to twenty minutes, and the maximum effect in from fifteen to fifty minutes; as a rule, the larger the dose the earlier the initial effect and the more delayed the maximum effect.

A greater amount of ouabain was necessary to reduce the ventricular rate in patients who had auricular fibrillation with elevation of temperature than in those without elevation of temperature.

The variation in dosage was less when calculated on the basis of body weight than on the basis of total dosage.

The persistence of action of the drug was variable in the cases observed, but in all except three the persistence was never longer than five days.

Mild toxic symptoms were noted in three of fifty-two instances in which full therapeutic effects were obtained.

It would seem that ouabain, if given in fractional doses, may be administered with safety intravenously to patients with auricular fibrillation that have not received digitalis recently.

When ouabain is given to patients with regular sinus rhythm, greater care must be used. In these patients clinical improvement seems to be the only criterion for full therapeutic effect; and since moribund patients may not show clinical improvement, there is greater danger of overdosage.

HOUSE DUST IN THE ETIOLOGY OF BRONCHIAL ASTHMA AND OF HAY-FEVER *

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House dust sensitization has gained increasing recognition in the etiology of bronchial asthma and hay-fever during the last four years. Hay, grain and feed dusts as well as dusts with which bakers, millers, wood workers and other artisans come in contact may also cause marked symptoms. However, attention in this article will be focused on house dusts that are the most important of this group.

LITERATURE

Kern [1] in 1921 first called attention to house dust sensitization, especially to the dust of bedrooms. He felt that many patients diagnosed by Walker as having nonsensitive asthmatic bronchitis were probably sensitive to house dust. He recommended routine tests with dust extracts especially in cases in which other skin tests were negative.

Cooke [2] in 1922 published his observations on house dust sensitization. He reported a case of asthma of fourteen years' duration in a man, aged 26, who gave no positive skin reactions except to dust extracts, and whose asthma was entirely controlled by eliminating the offending dust from his environment. Of 327 patients with asthma, 109 were found sensitive to his stock dust 1. Cooke predicted that dust extracts would be of definite diagnostic value in discovering etiologic substances in the environment of the patient. He felt that the active principle in dust was possibly a new, specific and unknown one.

Spivacke and Grove [3] in 1925 substantiated Cooke's idea that house dust contains a specific substance, rather than some common inhalation protein, such as that of horse dander. They felt, however, that there are many different dust atopens.

Grove and Coca [4] in 1925 found the ability of house dust and pollen extracts to give skin reactions unchanged after the probable removal of all nitrogenous substances by dialysis and tryptic digestion. From

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* Read before the American Association for the Study of Allergy, Dallas, Texas, April 18, 1926.

1. Kern, A.: Dust Sensitization in Bronchial Asthma, M. Clin. N. Amer. **5**:751 (Nov.) 1921.

2. Cooke, R. A.: New Etiologic Factors in Bronchial Asthma, J. Immunol. **7**:147-162 (March) 1922.

3. Spivacke, C. A., and Grove, E. F.: A Study of House Dust Atopen in Asthma, J. Immunol. **10**:465-469 (March) 1925.

4. Grove, E. F., and Coca, A. F.: A Study of the Atopens of Pollen, House Dust, Horse Dander and Green Pea, J. Immunol. **10**:471 (March) 1925.

such data they concluded that the active principle of dust and pollen extracts was not a protein and that of horse dander and green pea extracts was a protein.

Black [5] stated in 1926 that tolerance to the active principle of pollen can be obtained with apparently protein free extracts.

Alles,[6] however, feels that it is nearly impossible to be sure that a biologic solution contains no protein.

Brown [7] reported 47 reactors to dust extracts out of 100 patients with asthma.

Meyer [8] in 1923 reported 57 per cent of 235 asthmatic patients sensitive to dust extracts. Of sixty-one dust extracts tested, fifty-five gave positive skin reactions. He felt that house dust is the most common cause of bronchial asthma.

In 1925, Leopold [9] demonstrated the specific effect of house dust on patients with asthma who were sensitive to such dust. This work was carried out in a dust proof room in which the temperature, humidity and the type of dust in the air were under absolute control.

HISTORY

Patients will frequently give the history of coughing or sneezing or of hay-fever or asthma when in an atmosphere filled with house dust. One man with constant asthma for fourteen years dated his trouble from beating a carpet. Such patients avoid sweeping and cleaning, knowing that they are more comfortable if the dust is not disturbed. One college professor discovered that if his room was never cleaned and the windows never opened he was able to use it with the minimal coughing and sneezing. When cleaning was done, he had to absent himself from his room for several days.

Dust sensitization is so marked in many patients that they have symptoms from the small amount that is at all times suspended in the air of the ordinary home. Such patients will sneeze or cough if in a draught that raises dust in the air. I feel that certain asthmatic patients who develop asthma a few hours after retiring are probably sensitive not only to feather or other emanation proteins but also to the dust of their bedroom which gradually accumulates on the mucous mem-

5. Black, J. H., and Moore, M. C.: Pollen Therapy with Protein-Free Extracts, J. A. M. A. **86**:324-325 (Jan. 30) 1926.

6. Alles, G. A.: Pollen Therapy with Protein-Free Extracts, J. A. M. A. **86**:1151 (April 10) 1926.

7. Brown, A.: Present Day Treatment of Asthma, New York M. J. **118**:333, 1924.

8. Meyer, G. P.: House Dust in Asthma, Atlantic M. J. **27**:59-61 (Nov.) 1923.

9. Leopold, S. S., and Leopold, C. S.: Bronchial Asthma: A Study Under Controlled Conditions of Environment, Temperature and Humidity, J. A. M. A. **84**:731-734 (March 7) 1925.

branes until enough absorption occurs to cause symptoms. Such an explanation may be the real basis of the sneezing and coughing on arising from sleep. Dust sensitive patients are worse in the winter when they are confined more closely to their homes.

In my series of patients giving reactions to house dusts, 66 per cent gave histories suggesting such sensitization. It was noteworthy that men and children rarely gave such histories, probably because of lack of observation on their part.

HOUSE DUSTS AND THEIR EXTRACTS

House dust arises chiefly from materials of animal epidermal origin which furnish the home. Of these, feather pillows, hair mattresses, woolen blankets and carpets give rise to surprising amounts of dust.

TABLE 1.—*Reactions to Proteins in Ten Patients with Asthma Sensitive to Stock Dust 13* *

	Reactions to													
Case	Dust 13	Wheat	Eggs	Milk	Vegetable	Fruit	Spring Pollen	Fall pollen	Orris	Feathers	Horse	Cat	Sheep	Miscellaneous Animals
1	+++	0	0	0	0	0	0	0	0	+	+	0	0	+
2	+++	0	0	+	0	0	++	0	+	+	+	0	0	0
3	+++	++	0	0	0	0	+	0	0	+	0	0	0	+
4	+++	0	0	0	+	+	+	0	0	0	0	0	0	0
5	+++	0	0	0	0	0	+	+	0	+	+	0	0	+
6	+++	0	0	+	+	+	0	0	0	+	+	0	0	0
7	+++	0	0	0	0	0	0	0	+++	+	++	0	0	0
8	+	0	0	0	0	+	+++	+++	+	+++	+++	0	+	++
9	+	0	0	++	0	0	++	0	0	++	+++	+	+	++
10	++	0	0	0	0	0	+++	0	0	++	+++	0	0	+

* Protein tests are reported in groups, and many routine tests have not been included.

House dust may also contain rabbit and goat hair from upholstery, orris root from face powder, pyrethrum, glue, certain wood and matting dusts, as well as many others peculiar to each environment. To any of these, the allergic person may become sensitive. Cooke feels, however, that house dust contains a specific substance that has no relation to any of these obvious sources of dust. He supports this opinion by a table of reactions to other common proteins in dust sensitive patients which shows that patients reacting strongly to the same dust exhibit no uniformity in their reactions to other inhalant or food proteins.

I have indicated in table 1 the cutaneous reactions obtained with the routine testing of patients sensitive to the most active dust (dust 13). These data show no regularity in the skin reactions obtained in the various patients, though all but two gave reactions to proteins of feathers and horse dander and all but three reacted to pollen extracts.

The last three cases are of interest since they gave marked reactions to proteins of animal emanations and pollens, and less active results with the dust extract. In general, the multiplicity of types and number of sensitizations and the dissimilarity of skin reactions in allergic patients are illustrated. These results seem to support Cooke's idea of a new, specific principle in house dust, about the ultimate proof of which I am doubtful.

The patient sensitive to house dust must live in an environment entirely free from the dust as well as from other substances to which he gives reactions. From clinical experience, it must be assumed that the susceptible person can have symptoms from the slightest amount of that dust suspended in the air of his home. The delicacy of such sensitization

TABLE 2.—*Reactions of Patients to Their Own and Other Stock Dust Extracts* *

	Dusts Extracts*										
Case	1	2	3	4	5	6	7	13	14	16	10
1	0	0	—	—	D.	D.	—	—	—	—	0
2	D.	D.	0	—	—	0	—	+	0	0	0
3	0	0	0	—	—	—	—	—	—	—	0
4	+	+	0	+++	0	++	+++	+++	+	+	0
5	0	0	0	++	0	0	0	0	0	0	—
6	0	+	—	—	—	+++	0	—	—	—	0
7	0	0	0	0	0	0	0	—	—	—	0
13	0	+	0	0	0	0	+	+++	+	—	0
14	++	+	0	0	0	0	—	0	+	—	0
16	0	0	0	0	0	0	0	0	0	+++	0
10	0	0	0	0	0	0	0	0	0	0	0

* The reaction to the patient's own dust is underlined; — indicates that no test was made.

must be very great. Alexander, Becke and Holmes in 1926 demonstrated that typical anaphylactic reactions occurred in sensitive animals who inhaled a spray of the antigen, which experimentally affirms the importance of inhalants in the cause of asthma and hay-fever.

The extracts of house dust used have been prepared by extracting two or three amounts of such dust with the same extracting fluid, allowing two days at ordinary temperature for each extraction. For some months Coca's extracting fluid was used, but for the last eight months 0.5 per cent salt solution, as suggested by Piness,[10] has given a large number of active extracts. Such solutions have been sterilized by the addition of 0.3 per cent cresol and by Berkefeld filtration. Dust extracts have been prepared during the last year from dust from the houses of thirty-

10. Piness, G.; Miller, H., and Alles, G. A.: Comparative Methods of Protein Extraction, J. A. M. A. **83**:608-611 (Aug. 23) 1924.

two patients with hay-fever or asthma. Twenty of these have given good skin reactions and have been kept for stock solutions. Table 2 details the reactions of ten such patients to their own dust extract and to the extracts of each of the other nine patients. This table indicates that in those cases in which no skin reactions to any dust extract were obtained and in which a definite history of dust sensitization was present we probably did not extract the dust from the proper rooms of the patient's house. This also applies in those cases in which reactions occurred to other dust than their own. Case 4 gave large reactions to several dust extracts, including the autogenous one. Patient 16, however, gave no reactions except to her own extract. All of this supports the probability that house dust contains many, though possibly specific, active principles.

SKIN TESTING

The skin testing with dust extracts, as well as with other proteins, has been done with the scratch method. I found that active dust extracts give good skin reactions with this method, in many cases as large as the average pollen reaction. This report of the ability to obtain good reactions by the scratch method with dust extracts is the first definite one in the literature to date. The intradermal test, as recommended by Cooke, was used in the early testing with dusts, but I came to the conclusion that the scratch test gave as satisfactory evidence of dust sensitization. The absence of all constitutional reactions, the ease and rapidity of testing, and the ability to test a patient with at least fifty proteins at a sitting, make me a strong advocate of the scratch method. In this work, the retesting of certain patients who fail to give expected reactions to dust extracts has resulted in positive reactions. As stated in previous articles, these skin reactions have been interpreted as positive when an erythema or an irregular wheal larger than the control reaction is present. I feel that not all reactions indicate etiologic factors in the allergic problem of the patient, but that such reactions must be considered in the treatment until contrary proof is forthcoming.

BRONCHIAL ASTHMA

During the last year I have tested 160 new patients with asthma in my private work, with stock house dust solutions. Positive reactions to their own, or more often to stock, dust extracts have been found in seventy-three of this group. Thus, 45 per cent of my series gave dust reactions as compared with 47 per cent reported by Brown and 57 per cent by Meyer. My stock dust 13 gave positive reactions in 36 per cent of 122 patients tested, which compares with the reactions obtained by Cooke in 31 per cent of 327 cases tested with his dust 1.

The results of the routine testing of seventy of these dust sensitive asthmatic patients, with usually more than 200 common proteins, are

given in table 3. These data are presented for comparison in the same form as were similar data in a series of 234 patients [11] with asthma in all ages and 110 patients [12] with asthma in childhood and in young adult life, published in 1925.

The data given in table 3 show that this group of dust sensitive patients gave about the same relative number of skin reactions to foods as did patients in the two previous series. The percentage of patients reacting to total animal proteins and particularly to the feather, horse dander and sheep wool proteins is much higher. The percentage of pollen sensitive patients in this series is higher by 20 per cent than in my previous series. These results are probably due to the fact that I was dealing with asthmatic patients, all of whom were sensitive to inhalant dust proteins and all of whom gave skin reactions. The fact that 69 per cent of these

TABLE 3.—*Occurrence of Skin Reactions in Seventy Dust Sensitive Patients With Bronchial Asthma*

	Patients Giving Reactions			Patients Giving Reactions	
Food Proteins	Number of	Per Cent	Inhalant Proteins	Number of	Per Cent
Wheat	15	21	Dust	70	100
Corn	0	0	Feathers	47	69
Oats	3	4.5	Horse	28	41
Rice	0	0	Cat	10	15
Egg	7	10	Rabbit	18	26
Milk	7	10	Sheep	15	22
Fish	6	9	Silk	7	10
Nuts	2	3	Miscellaneous	23	34
Meats	2	3	Total animal	56	82
Fruits	7	10	Orris root	8	12
Vegetables	16	23.5	Tree pollens	7	10
Beverages	2	3	Spring pollens	36	53
Spices	1	1.5	Fall pollens	24	35
Total food	31	46	Total pollens	42	62

dust sensitive asthmatic patients reacted to feather proteins, 41 per cent to horse dander protein, 26 per cent to rabbit fur protein, and 22 per cent to sheep wool protein, and the fact that other animal emanation proteins gave many reactions make me feel that their reactions to house dust might be due to dusts arising from certain articles of furnishing rather than from some unknown source, as suggested by Cooke. The frequency of pollen reactions suggests that certain house dusts may contain pollen. In fact, the dust reaction might be a summation one due to slight sensitizations to various animal emanations, pollens or other substances present in the same dust extract.

The frequency of skin reactions to ten different house dust extracts in this series of seventy patients with asthma, as well as in a group of twenty patients with perennial hay-fever, is recorded in table 4. From this

11. Rowe, A. H.: The Treatment of Bronchial Asthma, J. A. M. A. **84**:1902-1905 (June 20) 1925.

12. Rowe, A. H.: Bronchial Asthma in Children and Young Adults, Am. J. Dis. Child. **31**:51-57 (Jan.) 1926.

table it is evident that certain dust extracts are more active in producing skin reactions than others. Out of this series of ten dusts, numbers 4, 13, 14 and 16 gave a high percentage of positive results. As pointed out before in table 2, however, no one stock dust gives reactions in all dust sensitive patients. This indicates the necessity of using a number of active dust extracts and autogenous extracts, when indicated in the study of the patient with a history of susceptibility to house dust.

The relative occurrence of dust sensitization according to age groups in these series of patients is recorded in table 5. It is especially interesting that 21 per cent of the patients with asthma were under 10 years of

TABLE 4.—*Percentage of Positive Reactions to Ten Different House Dust Extracts*

	Seventy Cases of Asthma			Twenty Cases of Hay-Fever		
Dust Extract	Number of Reactions	Number of Patients Tested	Percentage Giving Positive Reactions	Number of Reactions	Number of Patients Tested	Percentage Giving Positive Reactions
1	30	61	49	5	17	29
2	23	61	38	4	16	25
3	4	65	6	3	17	18
4	37	67	55	10	18	56.5
5	15	61	24.5	6	19	31.5
6	22	63	35	4	19	21
7	15	36	42	4	18	22
13	45	58	78	8	18	44
14	34	53	64	6	17	35
16	23	44	52	3	17	18

TABLE 5.—*Percentage of Dust Sensitive Patients with Asthma and Hay-Fever in Various Age Groups*

	Seventy Cases of Asthma		Twenty Cases of Hay-Fever	
Age Groups (Years)	Number of Cases	Per Cent	Number of Cases	Per Cent
0–10	15	21	3	15
10–20	10	14	2	10
20–50	37	53	14	70
50–80	8	11	1	5

age. The occurrence of dust sensitization in childhood and in youth, as well as in old age, is definitely reported for the first time in this table. It shows the importance of such sensitization and that no age is immune.

PERENNIAL HAY-FEVER

The patient who has slight or severe symptoms of hay-fever throughout the year always has been a problem for the specialist. Walker, in 1918, emphasized the importance of bacterial infection of mucous membranes as a cause of this trouble. In my experience, such bacterial infection, in the absence of sinusitis, is rarely the sole cause of coryza. Sinusitis, especially of the antrum, may cause symptoms suggesting hay-fever, but the absence of allergy in the family and personal history, and the absence of itching and sneezing and of skin reactions, would

indicate the absence of bacterial sensitization as a cause for nasal congestion. Sinusitis complicating allergic hay-fever may at times require surgery for relief. Vaccine therapy probably helps to increase resistance to such infection.

In patients who had perennial hay-fever, routine testing with stock and autogenous house dust extracts has demonstrated that dust reactions frequently occur in such patients and the definite importance of house dust in the etiology of this condition. I have tested such patients routinely with the proteins of all common foods, animal emanations, pollens, orris root, and with several active dust extracts. The results of the testing of twenty patients with all year round hay-fever are given in table 6.

An analysis of the skin reactions obtained in these patients who had perennial hay-fever and who were sensitive to house dust extracts indi-

TABLE 6.—*Occurrence of Skin Reactions in Twenty Dust Sensitive Patients with Hay Fever*

	Patients Giving Reactions			Patients Giving Reactions	
Food Proteins	Number of	Per Cent	Inhalant Proteins	Number of	Per Cent
Wheat	2	10	Dust	20	100
Corn	2	10	Feathers	13	65
Oats	1	5	Horse	6	30
Rice	1	5	Cat	4	20
Egg	2	10	Rabbit	1	5
Milk	1	5	Sheep	5	25
Fish	1	5	Silk	2	10
Nuts	2	10	Miscellaneous	7	35
Meats	1	5	Total animal	17	85
Fruits	4	20	Orris root	5	25
Vegetables	2	10	Tree pollen	0	0
Beverages	0	0	Spring pollen	14	70
Spices	1	5	Fall pollen	8	40
Total food	9	45	Total pollen	15	75

cates that sensitization to food and animal emanation proteins was about as frequent as in the series of dust sensitive patients with asthma. The frequency of pollen sensitization was greater than in the former series. This is probably due to the type of hay-fever occurring in California, where there is pollen in the air throughout ten months of the year. However, I included in this series only patients who had all year round hay-fever, excluding the large number of purely seasonal pollen cases. In spite of this fact, the multiplicity of types and number of sensitizations in patients who have perennial hay-fever and who are sensitive to house dust is demonstrated.

Single sensitization to orris root as a cause of perennial hay-fever is occasionally encountered. However, most patients who react to orris root also react to other proteins. The fact that food sensitization may also produce constant nasal congestion must be recognized.

An analysis of the reactions in this series shows that I could not be sure that dust sensitization alone was responsible for all the symp-

toms in any patient. Though the reactions to dust extracts in a few cases were stronger than those to other substances, each patient gave one or more slight or definite reactions to proteins other than those of dust. Thus, certain patients with all year round hay-fever were pollen sensitive and other patients with symptoms indicating only pollen sensitization have been found to have persisting trouble throughout the year, and have given other reactions as well to dust proteins. Thus, to do justice to the hay-fever patient who has even slight symptoms throughout the year, routine testing with a large number of proteins of all type should be done.

TREATMENT

House dust sensitization can often be controlled by a thorough cleaning of the living rooms, and especially the bedroom, of the patient. In most cases, furnishings made from animal hair and wool should be eliminated. Such procedure is usually effective if other sensitizations, such as food or pollen, are adequately controlled.

Those patients, however, who give marked reactions to house dusts may require desensitization to the active principles of several dusts in order to protect them. In certain cases it may be advisable to extract the dusts of several different rooms or of the upholstery or mattresses, in order to discover the actual source of dust sensitization indicated by history and skin testing. Treatment with such extract may then be advisable. The initial dose of a house dust extract should be 0.1 cc. of the dilution that just fails to give a skin reaction. In some cases, it has been necessary to start with a solution diluted 10, 50, 100 or, as in two cases, 3,000 times. Spivacke reports two severe constitutional reactions after the injection of 0.1 cc. of an undiluted extract. Such reactions must be prevented if possible.

VALUE OF TESTING AND TREATMENT WITH HOUSE DUST EXTRACTS

The main value of testing with dust extracts is in the indication of a type of sensitization active in the etiology of the patient's disease. Positive reactions to dust extracts should also make one suspicious of sensitization to other proteins, especially to animal emanation and pollen proteins, as demonstrated in the data in this article. Thus, the usual multiplicity of sensitizations in the patient with asthma or hay-fever must be kept in mind in the discussion of any one type such as I am considering here. House dust sensitization, however, is of great importance, and the positive dust reaction helps to demonstrate such sensitization to the physician and to emphasize the importance of the control of the house dust factor to the patient. I agree with Cooke and Meyer that such testing with dust extracts should be a matter of routine in all patients with asthma or perennial hay-fever.

The results obtained from the treatment with dust extracts are somewhat difficult to evaluate, since other types of sensitization were usually under control. However, my impression is that definite benefit was derived and that an attempt should be made to desensitize these patients with dust extracts to which they give strong reactions, especially if other skin reactions are small or indefinite.

CONCLUSIONS

1. It has been shown that 42 per cent of a series of 162 patients with asthma gave reactions to house dust extracts, and that twenty patients with perennial hay-fever also gave such reactions.

2. Dust reactions have been obtained in all age groups with the scratch test.

3. A large number of patients have a characteristic history of dust sensitization.

4. The necessity of testing with a large number of stock and autogenous dust extracts is demonstrated.

5. Dust reactions may depend on one substance or on a summation of lesser reactions to several substances, such as animal emanations, orris root, pollens, and various fabric dusts, and that the possibility of an unknown specific substance in house dust is unlikely.

6. The data collected show that reactions to dust rarely occur without one or more other reactions to proteins commonly used in testing.

7. Desensitization to house dust extracts which give definite reactions in the patient is probably advisable in cases in which a marked history of dust sensitization is present.

THE VALUE OF HISTAMINE AS A TEST FOR GASTRIC FUNCTION *

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Histamine (B-imidazolylethylamine) is derived from the amino-acid histidine, an almost universal constituent of proteins. It is evolved by decarboxylation in an appropriate medium by bacteria. Koessler and Hanke have shown that certain strains of *Bacillus coli* and other bacteria are capable of producing histamine from histidine in the presence of an available source of carbon such as glycerol or glucose, plus a source of nitrogen (potassium nitrate, ammonium chloride or both) in the presence of oxygen. They believe that histamine is formed in the bowel by bacteria in order to neutralize an excessive acidity produced from glycerol. These observers have shown that histamine is a normal constituent of the cecum and feces of man in sufficient amounts to be dangerously toxic. The reason for the absence of toxicity is not established definitely. Hanke and Koessler [1] believe that histamine is rendered pharmacologically inert in its passage through the intestinal wall. It is an exceedingly active substance physiologically, and when injected subcutaneously or intravenously, causes marked fall in blood pressure, dilatation of the superficial blood vessels and marked increase in gastric secretion. If given in sufficient dosage, symptoms of shock will ensue.

The only action of histamine with which we are concerned at present is its effect on gastric secretion. The manner in which gastric secretion is stimulated by the amine is not settled. Rothlin and Grundlach [2] maintain that its action is caused by vagus stimulation. Koskowski and Popielski [3] believe that it acts directly on the gastric secretory cells. Gutkowski,[4] in seeking to explain the latent period of stimulation, demonstrated that when histamine is slowly injected into the blood, it produces gastric secretion. He further found a gastric response after

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1. Koessler, K. K., and Hanke, M. T.: J. Biol. Chem. **39**:497 (Oct.) 1919.

2. Rothlin, E., and Grundlach, R.: The Influence of Histamine on Gastric Secretion, Arch. internat. de physiol. **17**:52, 1921-1922.

3. Popielski, L.: Histamine as a Strong Gastric Stimulant, Arch. f. d. ges. Physiol. **178**:214, 1920.

4. Gutkowski, B.: Stimulation of Gastric Juice of Slow Intravenous Injection of Histamine, Compt. rend. Soc. de biol. **91**:1345 (Dec.) 1924; Mechanism of the Action of Histamine in Promoting Gastric Secretion, Compt. rend. Soc. de biol. **91**:1349 (Dec.) 1924.

the subcutaneous injection of the drug into the posterior extremity of an animal whose only communication with the rest of the body was vascular. Ivy and Javois [5] have succeeded in producing histamine secretion in a "denervated" Heidenhain pouch, indicating that the mechanism of secretion is not nervous.

The effect of histamine on the human stomach was first observed by Carnot, Koskowski and Liebert [6] in 1922. On injecting from 0.75 to 1.75 mg. of the drug subcutaneously, they observed an increase in the flow of gastric juice in from thirty to fifty-five minutes, with an absolute increase in free and total acidity and in proteolytic activity. Matheson and Ammon [7] observed the effect of histamine on twelve convalescent patients. They used ergamine acid phosphate, which contains approximately one third of the base histamine. One and five-tenths milligrams of the salt was injected subcutaneously, and psychic stimulation was carefully avoided. They reported an increase in hydrochloric acid and in total acid starting in fifteen minutes, the maximum increase not being reached until from one-half to one hour after the injection. The maximum proteolytic activity as determined by the Mett method was reached earlier than the high acid level. They report a marked decrease in the amount of stomach mucus after injection of histamine in cases in which mucus was plentiful before the injection of this drug. This factor may influence the degree of acidity, according to these observers.

Lim, Matheson and Schlapp [8] corroborated the foregoing observations; they assert that histamine does not produce any direct effect on biliary or pancreatic secretion. They devised a method by which they prevented the entrance of gastric juice into the duodenum or duodenal secretions into the stomach. This observation was based on three cases. Gumpertz and Voorhaus [9] called attention to the value of histamine as an agent of differentiating true from pseudo-achylia. They injected 1 cc. of a 1:1,000 solution of the base subcutaneously and made extractions on the fasting stomach until the acid curve returned to normal. They report a marked response in normal persons as well as in persons with hypo-acidity. In a series of cases of supposed achylia gastrica, only 41 per cent turned out to be true achylia after injection of histamine. Dobson [10] observed the effect of histamine in seventeen

5. Ivy, A. C., and Javois, A. J.: Am. J. Physiol. **71**:604 (Feb.) 1926.

6. Carnot, P.; Koskowski, W., and Liebert, E.: Influence of Histamine on the Digestion Secretion in Man, Compt. rend. Soc. de biol. **86**:575, 1922.

7. Matheson, A. R., and Ammon, S. E.: Effect of Histamine on Human Gastric Secretion, Lancet **1**:482 (March 10) 1923.

8. Lim, R. K. S.; Matheson, A. R., and Schlapp, W.: New Gastro-Duodenal Technic, Edinburgh, M. J. **30**:262 (July) 1923.

9. Gumpertz, L. M., and Voorhaus, M. G.: Action of Histamine on Human Gastric Secretion, J. Lab. & Clin. Med. **11**:14 (Oct.) 1925.

10. Dobson, H. N.: Effect of Histamine on Gastric Secretion, J. A. M. A. **84**:158 (Jan. 17) 1925.

cases. The observations were made on fasting stomachs, and the secretion was analyzed up to one hundred and fifty minutes. He classifies his cases in three groups: (*1*) those in which hydrochloric acid is intermittently present, as shown by fractional analysis; (*2*) those in which hydrochloric acid is absent, as shown by the fractional method, but in which there is a definite response to histamine, and (*3*) those in which hydrochloric acid is persistently absent, as shown by both methods. Recently Carnot and Liebert [11] have advocated the superiority of the histamine test over the test meal for gaging gastric function. The absence of food prevents the fixation of the acid and ferment by the ingested protein. Their observations were made forty-five minutes after injection of 1 mg. of histamine.

We have been impressed with the difficulty in the diagnosis of achylia and interested in the mechanism of its production. The fractional gastric analysis as outlined by Rehfuss has been a routine procedure in our clinic for years. Even following this method of analyzing gastric function, we have been confronted with a great many borderline cases of achylia. In some instances a complete absence of mineral acid and enzyme was encountered, in others a transient trace of enzyme only was present and in still others an occasional trace of acid and enzyme occurred at one time, only to be absent at other times.

In this report an effort has been made to study the effect of injection of histamine on the gastric secretion when given simultaneously with the meal of bread and water. A comparison has been made between the gastric secretory response following the ordinary fractional analysis and the response after injection of histamine plus the test meal. In both instances extractions were made every fifteen minutes for two hours or until the stomach was empty. So far the reports on histamine are all based on an examination of the fasting stomach or one made after a water meal. In this study 1 mg. (1 cc. of 1 : 1,000 solution) of histamine (Hoffman, LaRoche) was injected subcutaneously after the insertion of the tube and the evacuation of the residuum simultaneously with the ingestion of the meal.

ACHLORHYDRIA

Twenty-one patients with so-called achlorhydria were examined in this manner, and the comparative secretory response can be seen in table 1. These cases were classified as achlorhydria following the fractional gastric analysis because of the absence of mineral acid throughout the two hour phase of gastric digestion. Ten patients were studied two or more times by the fractional method without the use of

11. Carnot, P., and Liebert, E.: Test Meals and Histamine Test for Determination of Secretory Activity of Stomach, Médecine **6**:657 (July) 1925.

TABLE 1.—*Achlorhydria Tested by Ordinary Fractional Gastric Analysis, Gastric Analysis Following Injection of Histamine and Excretion of Neutral Red*

	Fractional Gastric Analysis									Histamine			Neutral Red			
No.	Hydrochloric Acid	Acid	Enzyme	Hydrochloric Acid	Acid	Enzyme	Hydrochloric Acid	Acid	Enzyme	Hydrochloric Acid	Acid	Enzyme	Venous	Musc.	Remarks	Group
111	0	50	..	20	40	..	..	..	..	40	65	..	..	..	Groups 2 and 3 with ordinary gastric ferment	3
112	0	30	..	..	..	..	..	..	..	25	40	..	..	..	Groups 1 or 2 with ordinary gastric ferment	3
113	0	10	..	0	10	..	0	10	0	0	5	0	..	..	Alcoholic.....	1
114	0	10	+	0	30	+	..	..	..	0	25	+	+	0	Group 2 with ordinary gastric ferment	2
116	0	10	0	0	10	0	0	15	0	0	20	0	0	0	.....	1
117	0	15	..	0	10	0	..	..	..	0	35	0	0	0	.....	1
118	0	15	0	..	..	..	..	..	..	0	15	0	0	..	.....	1
121	0	20	0	0	15	0	0	24	0	0	..	0	..	..	.....	1
124	0	25	±	15	30	+	..	..	..	20	35	+	..	..	Groups 2 and 3 with ordinary gastric ferment	3
125	0	20	0	..	..	..	..	..	..	0	30	+	..	0	No acid; rennet with histamine	3
126	0	5	0	0	15	..	0	15	+	22	32	+	+	±	Groups 1 and 2 with ordinary gastric ferment	3
127	0	20	+	8	27	+	..	..	..	25	30	+	+	+	Groups 2 and 3 with ordinary gastric ferment	3
131	0	20	..	..	..	..	..	..	..	0	15	0	0	0	Cancerous stomach.....	1
132	0	20	0	..	..	..	..	..	..	5	25	+	+	..	Group 1 to ordinary.....	3
133	0	10	0	..	..	..	..	..	..	0	10	0	0	..	Combined lateral sclerosis.....	1
134	0	30	0	..	..	..	..	..	..	0	15	0	0	..	Pernicious anemia.....	1
135	0	20	0	..	..	..	..	..	..	0	15	0	..	..	Cancer.....	1
136	0	15	+	..	..	..	..	..	..	15	35	+	..	..	Group 2 with ordinary gastric ferment	3
137	0	15	0	..	..	..	..	..	..	0	10	0	..	..		
138	0	15	0	..	..	..	..	..	..	0	15	0	0	..	Bowel toxemia.....	1
141	0	5	0	0	10	0	..	..	..	5	20	+	+	..	Visceral syphilis, group 1 with ordinary gastric ferment	3

Diagnosis: Achylia, group 1; achlorhydria, group 2; hypochlorhydria, group 3; twenty-one cases.

histamine. In thirteen, the stomach's ability to excrete neutral red, after it had been injected either intravenously or intramuscularly, was tested. The figures recorded in the table under hydrochloric acid and acid represent the highest level of free acid and total acid during the test. The enzyme determination used was the simple milk test for rennet, a fifteen minute incubation period being followed. In the last column a final classification of cases has been made, based on all three examinations, that is, ordinary fractional analysis, fractional histamine analysis and neutral red test:

Group 1: True achylia gastrica, no hydrochloric acid or enzyme being present after ordinary fractional or histamine analysis, and absence of neutral red excretion by the stomach following its intravenous injection.

Group 2: Achlorhydria, no mineral acid after ordinary or histamine analysis, but a trace of enzyme following the ordinary or histamine test or both.

Group 3: Hypochlorhydria, reduced amounts of mineral acid and enzyme being present after injection of histamine.

Of the twenty-one patients in whom hydrochloric acid was absent on initial examination, five gave positive tests for gastric ferment (cases 114, 124, 126, 127 and 136). In case 126, free acid and ferment were absent during two fractional tests, but a faint trace of rennet was present in the third analysis. Almost invariably the enzyme in these cases was present only toward the end of the examination, from one and one-half to two hours after the meal. The literature contains innumerable cases classified as achylia, based on a single extraction made anywhere from one-half to one and one-half hours after a test meal.

Two of the five patients mentioned in the foregoing (cases 124 to 127) had hydrochloric acid on second analysis by the ordinary method. This is not surprising, since the figures for total acid were unusually high at the time of the first examination. These two cases were dropped from the achlorhydria group 2 to group 3 before the histamine test was used. A high total acidity was also obtained in case 3 during the first analysis. The second ordinary test revealed an acidity of 20. The injection of histamine into these three patients (cases 111, 124 and 127) caused a greater secretion of free and total acid, but they were dropped to group 3 before histamine was used. The fractional gastric analysis on two occasions in case 114 showed an absence of hydrochloric acid but a trace of enzyme. The injection of histamine did not cause any further response (no free acid was obtained). The neutral red test is of interest in this case. Injection of dye into the muscle did not cause any gastric excretion. After the intravenous injection of the dye, a trace appeared in the stomach. Although this case cannot be classified

as one of true achylia, because of the presence of rennet, histamine did not cause an acid response. This case remains in group 2. We think it possible that this patient had potential achylia. In cases 126 and 136 there was free acid in the stomach after injection of histamine, but none after the ordinary test. Injection of histamine dropped these cases from group 2 to group 3. The six cases under discussion do not belong to the true achylia group 1.

There remain fifteen cases which, after one or several fractional Rehfuss tests, did not show any hydrochloric acid or rennet. Of this series, which was potentially classified as belonging to group 1, four patients (cases 112, 125, 132 and 141) gave a gastric response to histamine. In case 125 there was enzyme after the injection of histamine but no free acid. It was placed in group 2. Both hydrochloric acid and enzyme appeared after histamine was used in the remaining three cases. They were lowered in the classification to group 3. The intravenous neutral red test was performed in cases 132 and 141. The dye appeared in the stomach, confirming the histamine test. Five patients (cases 112, 126, 132, 136 and 141) showed hydrochloric acid response to histamine when no acid was obtainable by the ordinary fractional method. In one patient (case 125), rennet was present after injection of histamine when both mineral acid and enzyme were absent after the Rehfuss test. Starting out with twenty-one cases which could have been classified as achylia gastrica by the factional gastric analysis as ordinarily performed (without enzyme determination), only eleven remain in that group, following injections of neutral red, histamine or both. Undoubtedly, if one hour extractions had been practiced instead of the fractional method over a similar period, a greater number of cases in which achylia was suspected would have been encountered. In a large number of our cases of hypochlorhydria there was neither acid nor enzyme one hour after the test meal was given. Table 1 demonstrates clearly the value of repeated fractional studies, as the original diagnosis of achlorhydria was discarded in six cases after a second or third test was made even before histamine was used.

Only eleven cases (53 per cent) withstood the critical studies to eliminate achylia gastrica. Injection of histamine did not produce any gastric response. Seven of the patients also received injections of neutral red, the dye not being excreted by the stomach. The neutral red determinations confirmed the histamine test in each case in which both were performed, with one exception (case 125). The dye was injected intramuscularly in this instance. It was not excreted by the stomach suggesting achylia, although enzymes were present after the ordinary and the histamine fractional test. This confirms our previous observation that the muscular injection of neutral red in the prescribed dosage

is insufficient to cause it to appear in some stomachs even in the presence of slight secretory function.[12]

HYPOCHLORHYDRIA

A similar comparison between the Rehfuss test and the histamine injection simultaneously with the test meal was made in twenty-nine cases of hypo-acidity. The degree of free and total acidity throughout both tests is compared in table 2. The composite free and total acid curves of these cases have been drawn, with and without the use of histamine (chart 1). It will be noted that hyponormal cases as a group

TABLE 2.—*Comparison Between Average Acidity, for Each Fifteen Minute Extraction, with Ordinary and Histamine Fractional Gastric Analysis*

Minutes after Meal	Hydrochloric Acid Ordinary Gastric	Hydrochloric Acid Histamine Gastric	Total Acid Ordinary Gastric	Total Acid Histamine Gastric
		Hypochlorhydria Group		
15	2.6	6.2	12.5	17.0
30	2.6	12.4	15.6	25.3
45	3.1	18.6	19.2	32.5
60	7.7	22.3	24.7	36.3
75	7.7	23.7	23.2	37.5
90	10.2	24.8	25.9	37.9
105	9.4	22.9	25.4	35.6
120	13.1	17.4	28.4	31.9
		Normacid Group		
15	7.3	16.0	21.5	27.7
30	11.1	26.8	25.6	42.3
45	21.3	34.5	38.2	49.5
60	30.9	40.5	49.6	60.4
75	31.2	40.6	51.5	60.0
90	30.0	37.0	50.0	53.5
105	24.0	40.0	49.4	56.7
120	34.0	35.0	51.0	52.5
		Hyperchlorhydria Group		
15	18.1	17.8	33.8	35.7
30	37.5	30.0	54.4	46.4
45	52.5	45.0	74.4	61.2
60	54.4	55.0	75.0	70.7
75	58.1	51.4	83.1	68.6
90	55.6	49.3	72.5	67.1
105	46.7	59.0	64.2	79.0
120	42.0	52.0	58.0	73.0

have a much higher secretory response after the use of histamine than after the Ewald meal alone. The higher secretion level for free and total acid starts before the fifteen minute extraction and persists for two hours. The highest level of histamine response is obtained from forty-five to one hundred and five minutes after the injection in this group. In twenty-two cases a comparison has been made between the appearance time and the duration of acid secretion by the ordinary fractional and histamine fractional methods (table 3). The average appearance time of hydrochloric acid after the ingestion of the Ewald meal was forty-eight minutes. When histamine was injected with the meal, the

12. Piersol, George Morris; Bockus, H. L., and Bank, J.: The Practical Value of Neutral Red as a Test for Gastric Secretory Function, Am. J. M. Sc. **170**:405 (Sept.) 1925.

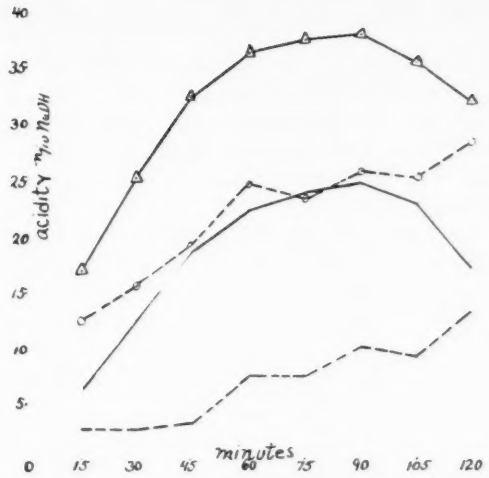

Chart 1.—Hypochlorhydria after injection of histamine. In these charts, the broken line indicates the free acid curve when histamine has not been injected; the dash and circle line, the total acidity; the solid line indicates the free acidity after the injection of histamine; the solid and triangle line, the total acidity.

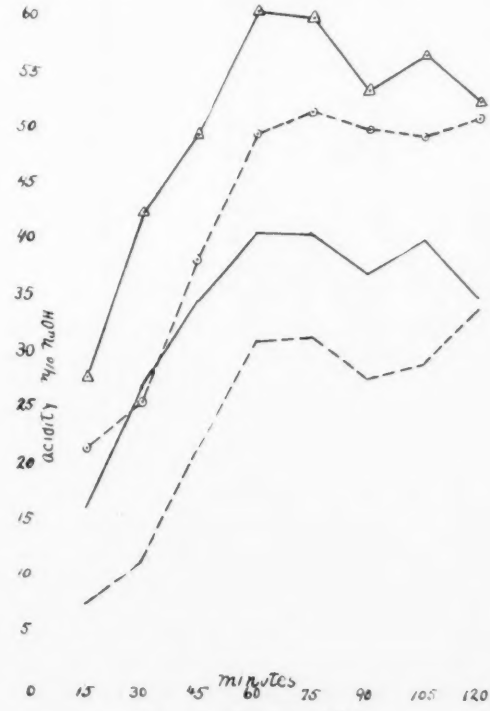

Chart 2.—Normal acidity.

average appearance time was shortened to thirty minutes. The average duration of the secretion curve following the meal alone was fifty minutes in this group as compared with seventy-eight minutes when histamine was injected simultaneously with the meal. Histamine in cases of reduced acidity causes the acid secretion to appear earlier and persist over a longer period.

In seven cases of hypochlorhydria which were achlorhydric to ordinary fractional test, injection of histamine caused free acid to make an average appearance in forty minutes and to persist for forty-one minutes. When these cases are compared with those included in table 3 which

TABLE 3.—*Hypochlorhydria: Comparison Between the Appearance Time and Duration of Acid Secretion During Fractional Gastric Analysis with and without Histamine*

	Ordinary Gastric		Fractional with Histamine	
Case	Appearance Time in Minutes	Duration of Secretion in Minutes	Appearance Time in Minutes	Duration of Secretion in Minutes
111	30	30–90	45	45–120
124	75	75–105	45	45–90
127	45	45–60	45	45–120
122	45	45–90	45	45–120
123	15	15–120	15	15–90
128	75	75–90	30	30–120
129	75	75–120	75	75–120
130	90	90–120	15	15–120
131	105	105–120	30	30–120
132	60	60–105	60	60–120
133	75	75–90	30	30–120
134	15	15–105	15	15–105
135	60	60–90	30	30–120
138	30	30–60	15	15–105
140	15	15–45	15	15–90
141	15	15–120	15	15–120
142	15	15–60	15	15–75
143	15	15–120	15	15–105
144	45	45–120	15	15–60
145	60	60–105	15	15–120
146	30	30–75	15	15–120
147	60	60–120	60	60–120
Group average	48	50	30	78

were hypochlorhydric after ordinary fractional, a definite trend downward in secretion is noticed. The acid appears later and persists for a shorter period in the former group (group 2 with ordinary fraction). Here is further confirmatory evidence of the gradual gradation between normacid and achylia stomachs.

NORMAL ACIDITY

Eleven cases approximating normal gastric acidity were compared in a similar manner (table 2). Most of these cases were possibly below normal in acidity but were considered too high to be included in the hypochlorhydria group. A composite curve of acidity in this group (chart 2) reveals an increase in degree of secretion when histamine was injected at the time of ingestion of the meal. The appearance time of secretion was earlier and the duration of secretion longer when histamine

was used. However, the secretory response to histamine was not nearly so great as in the hypochlorhydria group. It would appear that as the stomach secretion approximates normal, it responds less and less to histamine. Possibly it cannot secrete an acid greater than its high normal level.

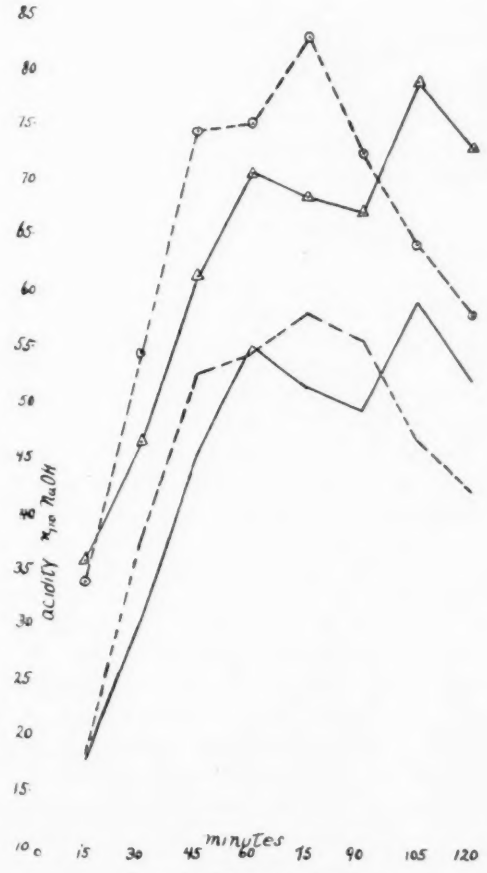

Chart 3.—Hyperchlorhydria.

HYPERCHLORHYDRIA

Injections of histamine were given to eight patients who were classified in the hyperacid group after ordinary gastric analysis. None of them had gastric stasis. No definite gastric pathologic change was diagnosed in any case. It will be seen by consulting the composite curve (chart 3) that the secretion was not increased after the use of histamine.

In fact, the free and total acid line with histamine is below the line of the ordinary fractional except at one hundred and five and one hundred and twenty minutes after the meal. This seems to be in accordance with Carlson's contention that the stomach cannot secrete an acid of more than normal concentration.

CONSTITUTIONAL EFFECT

We have not had any alarming reactions following the injection of 1 mg. of histamine. Almost invariably, the exposed parts of the body became red within a few minutes after the injection, and the blood pressure dropped on an average of 10 mg. of mercury. Occasionally a patient complained of headache. There was slight acceleration of the pulse rate. Only one patient, who had pernicious anemia, had a more severe reaction, and it was not alarming. She complained of extreme weakness and depression which lasted for several hours. An interesting observation was made of the physiologic action of histamine on another patient. The injection of histamine was given when he was under the influence of atropine mydriasis. Several minutes after the injection was given, his vision suddenly returned to normal.

SUMMARY

A comparison has been made between the ordinary fractional gastric analysis and a fractional analysis of the stomach following injection of histamine which was given simultaneously with the ingestion of the meal. This is the first time the effect of histamine on the stomach during the digestive phase with a carbohydrate meal has been studied. Space does not permit a discussion of a clinical or etiologic consideration of achylia gastrica. We consider achylia a rare entity, although hypochlorhydria and achlorhydria are encountered rather frequently.

1. Only 53 per cent of the stomachs in which achlorhydria was diagnosed after the Rehfuss test failed to secrete gastric juice after injection of histamine. However, in six of the twenty-one cases the diagnosis of achylia was discarded by repeated fractional tests.

2. The great bulk of literature on achylia gastrica is worthless. It is likely that only a small proportion of such cases which were reported previous to the last few years were really cases of achylia gastrica.

3 We believe that the diagnosis of achylia gastrica is impossible when the single extraction method is used.

4. Ordinary fractional gastric analysis, including enzyme determinations as well as acid titration, if frequently repeated, probably will be a safe method of diagnosing achylia in most cases. However, there will remain a few cases in which acid or enzyme will not be found by this method, but in which there will be a secretory response to histamine.

5. In the present state of our knowledge of achylia, the diagnosis had better not be made definitely without confirmation by the histamine test.

6. The failure of the stomach to excrete neutral red after its intravenous injection has proved equally reliable in the diagnosis of achylia in our hands.

7. In cases of hypochlorhydria injection of histamine caused a definite increase in the acidity throughout the period of gastric digestion of the Ewald meal. It caused mineral acid to appear earlier and prolonged the period of secretion.

8. In cases of normal acidity, injection of histamine caused an elevation of the degree of acidity, but to a lesser extent than in cases of reduced gastric acidity.

9. In cases of hyperacidity, the stomach did not respond to the subcutaneous injection of histamine.

10. Histamine proved safe in our hands, and we believe it is of distinct value in the differentiation between achylia and achlorhydria or hypochlorhydria.

11. We do not believe that injection of histamine with or without a water meal is in any way comparable to the fractional gastric analysis as a general test for gastric function. We believe with Rehfuss that the fractional method yields information as to gastric work, and that a definite load must be imposed on the stomach in order to judge its ability to perform its function. The normal physiologic load is food, and that substance must be used in order to get the maximum information concerning the secretory and motor function. We feel that the performance of the ordinary fractional gastric analysis and the histamine gastric analysis as described will yield more information than either alone in stomachs with a low acidity, and that both tests should be made in such cases.

THE COURSE OF HYPERTHYROIDISM UNDER IODINE MEDICATION *

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When the iodine remission in hyperthyroidism is complete, it is one of the most striking of therapeutic transformations. The process is now well known.[1] During an investigation of this remission in 1923,[2] two other associated reactions of hyperthyroidism to iodine were noted; namely, the gradual return of the disease during continued iodine administration, when there was no operative intervention, and the sudden exacerbation after the iodine was stopped. Repeated clinical experiences with these three phenomena have led to the impression that they form a sequence through which the disease will pass when the patient is treated with daily doses of iodine for a definite period. This whole course cannot be experimentally studied in patients, since it must be interrupted by thyroidectomy; but the regularity with which recurrence and postiodine reaction occur when the opportunity arises leaves little doubt that they are constant phases of the effect of iodine on the course of hyperthyroidism. The material covering these undesirable phases is necessarily limited to clinical mistakes, especially to those instances in which the actual course can be demonstrated by determinations of the metabolic rate.

Only one small part of this process, the iodine remission which occurs during the first few days, is of any practical value. The remaining weeks under iodine medication and several weeks after the iodine is stopped are occupied by the reestablishment of the disease. Hence, unless the remission is to be used as a period for operation, the administration of iodine to patients with hyperthyroidism is without final benefit, and usually harmful. Many of the patients coming to this clinic have been given iodine for a long time, and thus the opportunity for the best preoperative preparation by the primary iodine remission

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* From the Medical Department of Northwestern University Medical School. Cases studied are from the services of Dr. Charles A. Elliott, Dr. Allen B. Kanavel and Dr. Harry M. Richter at the Wesley Memorial Hospital.

1. Plummer, H. S.: Results of Administering Iodin to Patients Having Exophthalmic Goiter, abstr. J. A. M. A. **80**:1955 (June 30) 1923. Plummer, H. S., and Boothby, W. M.: Value of Iodin in Exophthalmic Goiter, J. Iowa M. Soc. **14**:66 (Feb.) 1924. Starr, P.; Segall, H. N., and Means, J. H.: Effect of Iodin in Exophthalmic Goiter, Arch. Int. Med. **34**:355 (Sept.) 1924. Cowell, S. J., and Mellanby, E.: Effect of Iodin on Hyperthyroidism in Man, Quart. J. Med. **18**:1 (Oct.) 1924. Fraser, F. R.: Iodine in Exophthalmic Goiter, Brit. M. J. **1**:1 (Jan. 3) 1925.

2. Starr, P.; Segall, H. N., and Means, J. H.: Effect of Iodin in Exophthalmic Goiter, Arch. Int. Med. **34**:355 (Sept.) 1924.

has been lost. If the physician wishes to cooperate with the surgeon in the treatment of patients with this condition, he should not administer iodine as a cure. It cannot benefit his patient permanently.

THE COMPLETE IODINE EFFECT

The typical complete course (as represented by the basal metabolic rate) in all types of hyperthyroidism, when the patient is treated with daily large doses of iodine in any form, is illustrated in chart 1. The process consists of three stages: First, there is a remission of the disease; this has been found by many observers.[1] Second, there is a recurrence under continued iodine therapy.[3] Third, there is a postiodine reaction consisting of a self-limited period of increased metabolism, after which the rate returns to the level established before iodine was given.[2]

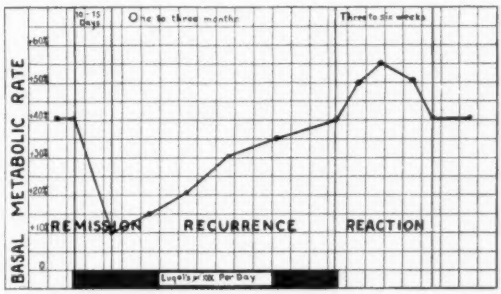

Chart 1.—The metabolic rate in hyperthyroidism under administration of iodine and after it is discontinued. It is assumed that the metabolic rate before iodine is about + 40 per cent; the remission then occurs rapidly, and as here represented, is complete; the recurrence is more gradual; and after the iodine is stopped, there is a sharp self-limited period of increased metabolic rate, the postiodine reaction. The time periods given are only approximate.

Chart 1 illustrates the iodine action when fully effective. There is, however, every gradation of this effectiveness, from those cases in which the metabolic rate is entirely unchanged by the usual dosage of iodine, to those in which the disease seems to stop suddenly when iodine is administered. Occasionally, the recurrence seems long and gradual, only to be followed by the postiodine reaction when the iodine is discontinued. The postiodine reaction may be characterized by a degree of hyperthyroidism not present before the iodine was given. It occurs following remission and also after recurrence.

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3. Starr, P.; Segall, H. N., and Means, J. H.: Effect of Iodin in Exophthalmic Goiter, Arch. Int. Med. **34**:355 (Sept.) 1924. Cowell, S. J., and Mellanby, E.: Effect of Iodin on Hyperthyroidism in Man, Quart. J. Med. **18**:1 (Oct.) 1924. Fraser, F. R.: Iodine in Exophthalmic Goiter, Brit. M. J. **1**:1 (Jan. 3) 1925.

THE IODINE REMISSION

In a previous paper,[2] the frequency of occurrence of the iodine remission in a series of patients with hyperthyroidism was given as 80 per cent; Plummer [4] had reported a similar and even greater frequency, but it must be emphasized that there will be great variation in the extent of remission. An analysis of thirty-six cases in which the patients were recently observed is presented in table 1. This group is unselected and includes patients with every type of hyperthyroidism, of widely different ages and with many varieties of pathologic changes in the thyroid gland. In eight (first two groups) or about one fourth of the thirty-six, there was little or no remission, while in twenty-eight (the remaining groups) or about three fourths, there was a reduction in the metabolic rate of 50 per cent or more. In cases showing little

TABLE 1.—*Frequency and Degree of Iodine Remission. Analysis of Data of Thirty-Six Unselected Clinic Patients Exhibiting All Types of Hyperthyroidism*

Reduction of Metabolic Rate to Normal, Percentage	Number of Patients	Average of All First Metabolic Rates, Percentage	Average Period Under Iodine, Days	Average Dose of Lugol's Solution Daily, Minims	Average of All Last Metabolic Rates, Percentage
0	4	+53	12	45	+53
25	4	+51	7	30	+37
50	15	+67	12	30	+36
75	9	+55	11	45	+20
100	4	+60	15	30	+ 8

reduction of metabolic rate there is often a gain in weight and a slowing of pulse, with general clinical improvement indicating that there is a true remission, although of slight grade, in progress. Including such cases, the frequency of remission is probably over 90 per cent. Since only thirteen, or about one-third of this group, have a remission approaching normal, the postponement of operation in the hope of complete reduction of metabolic rate must not be delayed after the average period usually necessary for induction of the iodine remission. This period has been shown to be from ten to fifteen days. Recurrence begins gradually after this. The total period of low metabolic rate varies from a few days to three weeks. The actual reversal of the remission probably begins immediately after it is complete.

IODINE REMISSION IN NONEXOPHTHALMIC HYPERTHYROIDISM

It has previously been shown that the iodine remission occurs in cases of hyperthyroidism clinically described as exophthalmic goiter.[2] From an analysis of recent clinical material, it is evident that cases of

4. Plummer, H. S., and Boothby, W. M.: Value of Iodin in Exophthalmic Goiter, J. Iowa M. Soc. **14**:66 (Feb.) 1924.

hyperthyroidism of the chronic type, which are not exophthalmic goiter, are also subject to the iodine remission. This conclusion comes as a result of using Lugol's solution in preoperative preparation in every variety of hyperthyroidism, and it is evident that any distinction concerning the primary iodine effect is not to be made between exophthalmic goiter, toxic goiter, or adenomatous goiter with hyperthyroidism.

In table 2 the remissions in twenty patients with toxic goiter and adenomatous goiter with hyperthyroidism are classified on the same basis as in table 1. It is to be noted that five, or one-fourth, had a remission of 25 per cent, or less, while fifteen, or three-fourths, had a remission of 50 per cent or more. Thus, the frequency and extent of remissions in this group is the same as for the unselected group and practically the same as for the series of patients with exophthalmic goiter which was reported previously.[2]

TABLE 2.—*Remissions in Twenty Patients with Toxic Goiter, Including Adenomatous Goiter with Hyperthyroidism*

Extent of Reduction of Metabolic Rate, Percentage	Number of Cases
0	2
25	3
50	7
75	7
100	1

A typical 75 per cent remission occurred in the following case:

Mrs. C. M., aged 46, had had slight enlargement of the thyroid body for several years; there was a palpable nodule in the left lobe. Following an infection of the leg two years before entrance, she complained of weakness, dyspnea and palpitation. On examination, exophthalmos was not found, and auricular fibrillation was present. The basal metabolic rate was + 38 per cent. After fourteen days, during which 20 minims of Lugol's solution was given each day, the rate was + 16 per cent, practically a complete remission. Pathologic report after thyroidectomy was differentiated fetal adenoma of the thyroid.

The other cases classified in table 2 are entirely analogous to this. The average age of the patients was 46 years; exophthalmos was not present; cardiac symptoms were predominant; there were five patients with auricular fibrillation; pathologic reports are uniformly of adenomas or adenomatous growth.

In chart 2 are presented the metabolic rate curves of seven patients whose clinical history and physical and pathologic examination showed an adenomatous goiter with hyperthyroidism. The primary iodine remission occurred in all of these patients. The average decrease of metabolic rate under iodine was thirty points. As a result of this experience, the statement that the primary iodine remission occurs and may be complete in all types of hyperthyroidism seems justified.

ABSENCE OF IODINE REMISSION

The converse of this is the fact that iodine, as used in this work, that is, in doses of from 15 to 45 minims of Lugol's solution a day, has occasionally failed to produce remission in every clinical type of hyperthyroidism. The data of a group of five patients with exophthalmos and hyperplastic thyroids have been published previously.[2] Although clinically and pathologically representative of exophthalmic goiter, they did not have the primary iodine remission. In a more recent study, the metabolic rate curves and the characteristics of patients with all types of hyperthyroidism who had only a 25 per cent remission or less, are shown in chart 3. The ages range from 38 to 65 years; the goiter was imperceptible in two, and had been present from three months to thirty years in the others; the symptoms had been present an equally variable length of time; exophthalmos was absent

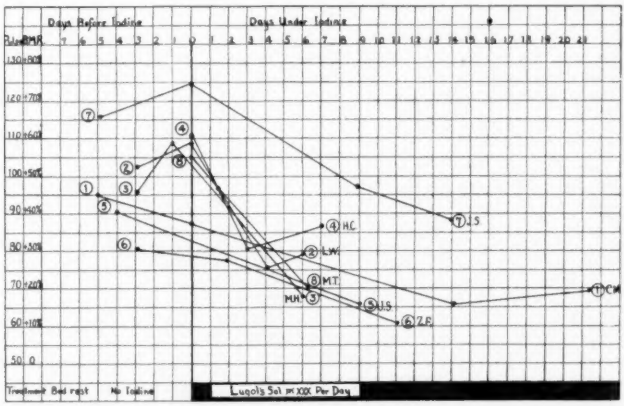

Chart 2.—Effect of iodine on metabolic rate in adenomatous goiter with hyperthyroidism. Eight patients showed iodine remission: *1*, aged 46, duration of goiter not known definitely, duration of symptoms two years, exophthalmos not present, pathologic report; fetal adenoma; *2*, aged 46, duration of goiter ten years, duration of symptoms twenty years, exophthalmos not present, pathologic report: adenoma of thyroid; *3*, aged 55, duration of goiter five years, duration of symptoms five years, exophthalmos not present, pathologic report: adenoma of thyroid; *4*, aged 52, duration of goiter more than two years, duration of symptoms five years, exophthalmos not present, pathologic report: multiple adenomas; *5*, aged 52, duration of goiter thirty-five years, duration of symptoms five years, exophthalmos not present, pathologic report: fetal adenomas; *6*, aged 62, duration of goiter more than four years, duration of symptoms seven years, exophthalmos not present, pathologic report: degenerating adenomas; *7*, aged 62, duration of goiter three years, duration of symptoms three years, exophthalmos not present, pathologic report: colloid goiter, adenomatous growth; *8*, aged 52, duration of goiter not known definitely, duration of symptoms two years, exophthalmos not present, pathologic report: colloid adenoma. Operation followed the last determination in all cases.

in three, and marked in one; the pathologic change ranges from marked acute hyperplasia to multiple adenomas. There would seem, so far as these observations are concerned, to be no clinical or pathologic features characteristic of these processes which are resistant to iodine medication as compared with those which yield to this therapy.

To summarize the data relative to the iodine remission: (*a*) A more than 50 per cent reduction of basal metabolic rate may be expected in at least three fourths of all patients with all types of hyperthyroidism, including adenomatous goiter with hyperthyroidism, within fifteen days, when from 15 to 45 (0.9 to 2.8 cc.) minims a day of Lugol's solution is first given; (*b*) in about one fourth or less of all patients with whatever type of hyperthyroidism, there will be less than a 25 per cent reduction of metabolic rate; (*c*) no clinical or pathologic characteristic distinguishes these processes resistant to iodine, as it is now used, from those which yield to iodine.

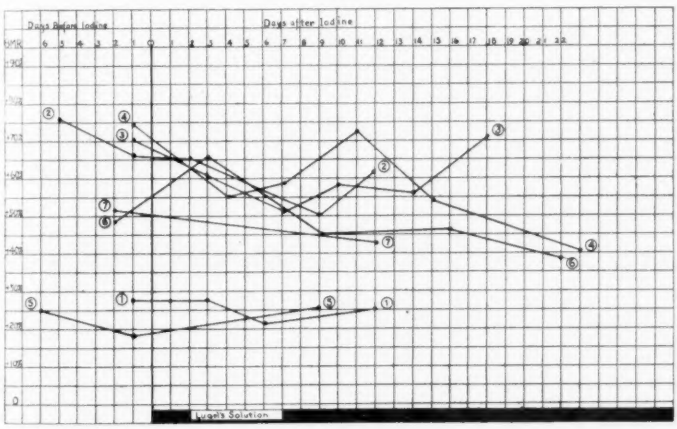

Chart 3.—Examples of absence of iodine remission. Metabolic rate curves: *1*, aged 59, duration of goiter not known definitely (small), duration of symptoms seven years, exophthalmos not present, pathologic report: slightly adenomatous growth on colloid thyroid; *2*, aged 65, duration of goiter thirty-two years, duration of symptoms twenty years, exophthalmos not present, pathologic report: colloid adenoma of thyroid; *3*, aged 41, duration of goiter three months, duration of symptoms three months, exophthalmos ±. Pathologic report: hyperplastic thyroid, moderate, marked; *4*, aged 47, duration of goiter two years, duration of symptoms two years, exophthalmos ++, pathologic report: diffuse adenomatous colloid goiter; *5*, aged 39, duration of goiter ten years, duration of symptoms two years, exophthalmos not present, pathologic report: multiple colloid adenomas; *6*, aged 40, duration of goiter not known definitely (small), duration of symptoms nine years, exophthalmos +++, pathologic report: acute hyperplasia, marked; *7*, aged 38, duration of goiter nine months, duration of symptoms nine months, exophthalmos +, pathologic report: moderate and marked hyperplasia. Lugol's solution, 10 minims (0.6 cc.) three times a day began on zero line.

RECURRENCE UNDER IODINE MEDICATION

The demonstration that after the iodine remission, even though iodine is continued, there will be a more or less gradual and immediate return of hyperthyroidism rests on experimental results and clinical experience. In the fall of 1923, a group of five patients at the Massachusetts General Hospital, who had had good remissions with iodine, was again given this medication in order to determine the possibility of continuous iodine control (chart 4). At the end of the second or third month, in all of these patients the metabolic rate was equal to the rate before iodine was given. A subtotal thyroidectomy was ultimately successful in all of them, so that the postiodine reaction could not be demonstrated. Four months had been wasted in an unsuccessful attempt to control the disease by iodine. Such detailed and measured proof

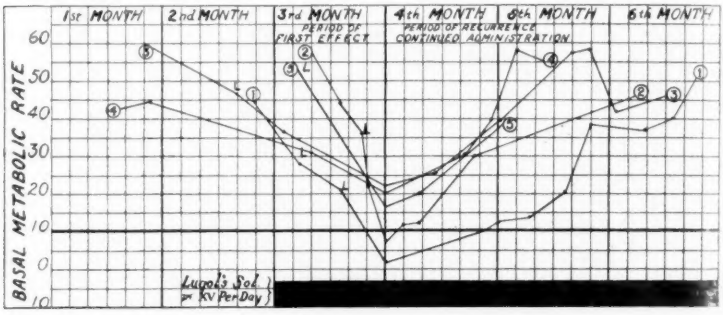

Chart 4.—Remission and recurrence under iodine.

that recurrence always follows remission is not abundant. In clinics in which iodine is used intelligently, operation interrupts hyperthyroidism before recurrence takes place. Occasionally, however, owing to a misconception of the course under iodine, such a demonstration occurs.

A recent case may be added to these. The metabolic rate of Mr. L. K. fell from + 75 per cent to + 11 per cent in fifteen days under the administration of Lugol's solution. It was thought that the disease must have been abated permanently. The patient was discharged with orders to continue the same dosage. During the next six weeks, although he gained weight, the basal pulse rate rose from 65 to 100, and the metabolic rate readings were successively + 19 per cent, + 35 per cent, and + 47 per cent. It was evident that the disease had recurred in spite of the continuation of iodine therapy, and without further delay subtotal thyroidectomy was performed.

Additional evidence in favor of recurrence during treatment with iodine is found in a study of the previous medication given to patients with hyperthyroidism who finally came to the hospital for thyroidectomy. Of a recent series of seventy-five patients who were subjected to the

maximal thyroidectomy, twenty-five had received iodine for from three weeks to nine months before entrance. Some of these are instances of induced iodine hyperthyroidism; most of the patients had the disease before the iodine was given. It is chiefly because of these patients, in whom the opportunity for the primary iodine remission had been passed because of the mistaken practice of their physicians or themselves, that this report is published. A typical example may be cited:

Mrs. V. der W., aged 34, felt the onset of her second attack of hyperthyroidism six months before seeking medical attention. The metabolic rate on January 15 was + 63 per cent; on March 25 it was + 71 per cent; administration of Lugol's solution was started on March 27; on April 10 the rate was + 15 per cent, and on April 20 it was + 13 per cent. Although this was the optimal time for operation, it was decided to have the patient come to Chicago, and the operation was postponed, although she continued to take

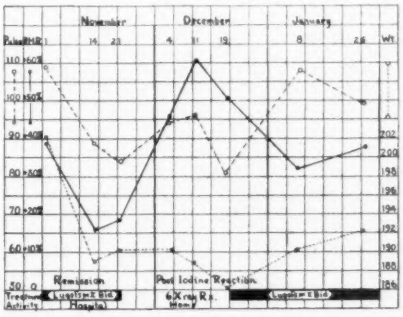

Chart 5.—Postiodine reaction occurring immediately after remission. Mrs. C. M., chronic hyperthyroidism, pathologic report: adenoma of thyroid.

iodine until May 20. On May 29, the rate was + 52 per cent. The opportunity for operation during the iodine remission, which in this case was nearly complete, had been lost.

To summarize: (*a*) Iodine cannot, as it is now given, control hyperthyroidism indefinitely. It should be used only for its primary effect; that is, as a preparation for operation. Recurrence follows remission, usually beginning within three weeks after the first administration of iodine.

POSTIODINE REACTION

Still further proof that iodine does not cure hyperthyroidism is the phenomenon known as the postiodine reaction. Examples of this are numerous. It is well recognized that if the medication is discontinued at the end of the remission, reaction to the original rate or even to a higher rate will occur rapidly. Hence, in clinical use the control by iodine must be continuous before, throughout and after the operation.

In the case illustrated in chart 5, a remission in a patient with adenomatous goiter with hyperthyroidism had brought the metabolic rate in fourteen days from + 38 per cent to + 16 per cent; because of the severity of the cardiac condition, operation was postponed, and the iodine was discontinued; during the next twenty-seven days, the metabolic rate rose to + 60 per cent and then spontaneously fell to + 50 per cent. Another example is afforded by the course in the case of Mrs. M. F. The metabolic rate fell from + 82 per cent to + 21 per cent under treatment with Lugol's solution, after which ligation was performed. Iodine was then discontinued in order that the effect of this operation might be observed. A postiodine reaction then occurred with a rise of rate in ten days from + 21 per cent to + 53 per cent, the pulse rate rising from 82 to 113.

It is not so well recognized that when iodine administration has been associated with a recurrence or continuation of mild hyperthyroidism, or

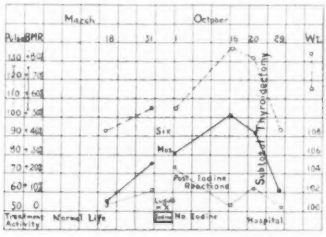

Chart 6.—Postiodine reaction after six months of iodine. Note tachycardia and loss of weight. Miss B. H., aged 18, pathologic report: acute hyperthyroidism; incorrect procedure.

is without apparent effect, that if it is then stopped, a temporary exacerbation of symptoms and rate occurs, which may be severe. Four examples of the postiodine reaction during recurrence or in the absence of remission were given in the previous paper;[2] two typical examples, one studied deliberately, are given here. Furthermore, the crises illustrated in charts 8 and 9 are in accordance with the history of postiodine reactions.

In the case illustrated in chart 6, the presence of mild hyperthyroidism was suspected because of tachycardia; without iodine the metabolic rate rose from + 8 per cent to + 27 per cent; then, with the mistaken idea that small doses of iodine would abort this mild attack, 10 minims (0.6 cc.) a day of Lugol's solution was given; at the end of six months, the rate of thyrotoxicosis was about the same. Iodine was then stopped, and during the next fifteen days hyperthyroidism increased to such an extent that the basal metabolism rate was + 50 per

cent, the tachycardia over 130, and the weight gained during the preceding six months was abruptly lost. The disease passed from a condition of partial control to one of unchecked activity.

A young girl with a colloid goiter had been treated with iodine at home for two months (chart 7). When the patient entered the hospital, Lugol's solution was ordered immediately, and with rest, the rate fell from + 90 per cent to + 56 per cent; during the next two weeks no material change occurred, although there was a marked gain in weight. It was then decided to allow the postiodine reaction to occur in the hope that after it had run its course, an iodine remission could be produced. When the medication was stopped, the metabolic rate rose during the next twenty-seven days from + 56 per cent to + 74 per cent, and there was a corresponding tachycardia. The rate then fell spontaneously to + 52 per cent; when iodine medication was again started, a remission occurred; the rate dropped to + 23 per cent. Subtotal thy-

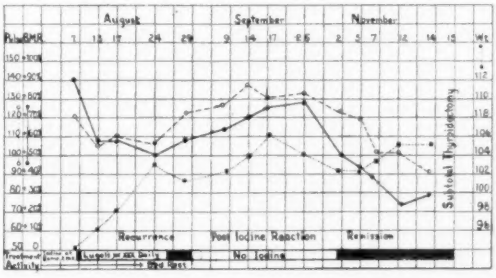

Chart 7.—Postiodine reaction at the end of recurrence. Complete self-limited course of postiodine reaction shown. All three stages of iodine effect in hyperthyroidism illustrated. Miss E. A., aged 16, acute hyperthyroidism, pathologic report: colloid goiter and hyperplasia.

roidectomy was then successfully accomplished. This case constitutes further demonstration of the postiodine reaction, bringing out especially that it may occur even if iodine is at the time unable to lower the metabolic rate materially.

Another example illustrates the possibility of the postiodine reaction after prolonged iodine control. On examination, Mr. G. D. presented marked exophthalmos, but a metabolic rate of + 12 per cent. He had received iodine for six months before this; it had been started as treatment in acute hyperthyroidism. Unfortunately, the diagnosis was questioned, and the medication stopped; seven days later, the metabolic rate had risen to + 53 per cent, with corresponding tachycardia.

Experience with a case of induced hyperthyroidism described below indicates that the thyroid condition in iodine hyperthyroidism is not an

exception to this rule; postiodine reaction occurs when the iodine is stopped, even when it has been responsible for the presence of hyperthyroidism. It may be stated as a general rule, experimentally demonstrated and repeatedly observed, that when a patient with hyperthyroidism has received iodine medication, whether or not the remission or recurrence is then in progress, an increase in metabolic rate and an exacerbation of symptoms occur during the succeeding days or weeks when the administration of iodine is suddenly stopped.

THYROTOXIC CRISES

Perhaps the most dramatic use of iodine in hyperthyroidism is in the control of severe thyrotoxic crises. It was for this especially that Plummer introduced the administration of large doses. If iodine is used consistently and continuously before, during and after the opera-

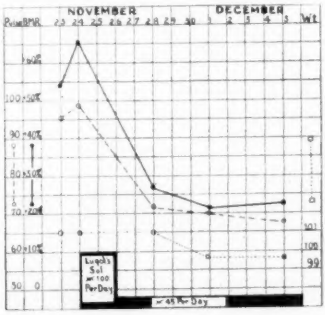

Chart 8.—Control of thyrotoxic crisis occurring as a postiodine reaction in a patient with an adenomatous goiter with iodine hyperthyroidism. Mrs. M. S., adenomatous goiter; gastric crisis.

tive period, it is rare to see these crises. In two instances in which iodine was not given postoperatively, crises occurred. Apparently, crises which are essentially postiodine reactions occur immediately after the operation. The optimal period over which to continue iodine medication after the operation is not definitely known; it is about two or three weeks. Segall and Means [5] have shown that the immediate effect of subtotal thyroidectomy is complete in ten days.

A recent example of what Dr. Arnold S. Jackson has emphasized as iodine hyperthyroidism [6] is given in the following case (chart 8). It again shows the postiodine reaction.

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5. Segall, H. N., and Means, J. H.: Immediate Effect of Subtotal Thyroidectomy in Toxic Goiter; Daily Basal Metabolism and Pulse Observations, Arch. Surg. **8**:176 (Jan.) 1924.

6. J. Jackson, A. S.: Iodine Hyperthyroidism, Am. J. M. Sc. **170**:271 (Aug.) 1925.

Mrs. M. S., aged 50, had vomited constantly for five days; she complained of abdominal distress; she had lost 25 pounds (11 Kg.) during the previous seventeen days. Until then, she had been taking iodine tablets because of difficulty in swallowing, said to be caused by an inward goiter; she had begun this treatment eight months previously. Physical examination revealed an emaciated, nervous woman; exophthalmos not present; a slightly enlarged thyroid gland; a pulse rate of 90; weight, 101 pounds (46 Kg.); blood pressure, systolic 180, diastolic 96. The basal metabolic rate was +54 per cent; the next day it was +66 per cent. The patient was observed in the hospital for three days; she vomited frequently and was able to take only small amounts of liquid. She was then given 100 minims (6 cc.) of Lugol's solution by rectum in two doses; and during the next day, ten doses of 5 minims (0.3 cc.) of Lugol's solution by mouth, all of which she retained. During this day she did not vomit, and ate light food; on the next day she ate three meals, including meat, potatoes and pumpkin pie. Fifty minims (3 cc.) of Lugol's solution were given on this

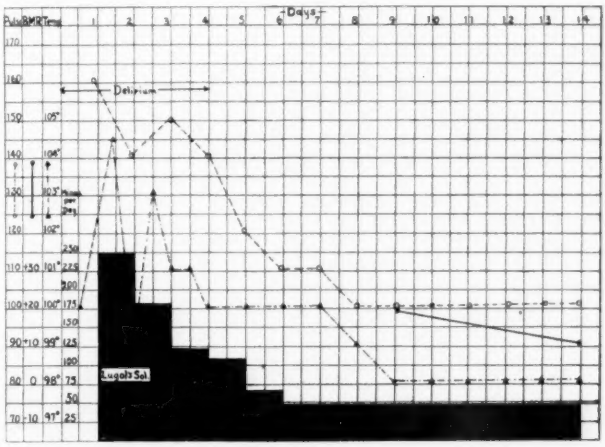

Chart 9.—Control of acute thyrotoxic crisis occurring as a postiodine reaction after complete remission. Large dosage of Lugol's solution.

second day; thus in forty-eight hours she received 200 minims (12 cc.) of Lugol's solution. Two days later the metabolic rate was +27 per cent. Subtotal thyroidectomy was later successfully accomplished. The pathologic report was "colloid goiter with moderate diffuse adenomatous growth."

A similar but more striking example of a violent thyrotoxic crisis occurring as a postiodine reaction may be cited in the following case:

Mr. L. O., a young white man, was admitted to the hospital in a delirious condition on June 16. The parents said that he had had a goiter for several years. In February he became nervous, and his eyes began to bulge. It is evident from this history that hyperthyroidism was already in progress. A metabolic rate determination was made on May 17. This was + 25 per cent. Five grains (0.3 Gm.) of potassium iodide was taken three times a day from May 18 until after the second metabolic rate measurement on May 28. This was — 9 per cent. The administration of iodine was then stopped. On June 13 the patient became

dizzy, had a headache and was nauseated. During the next three days, he became progressively more restless and irritable. When first seen he was delirious and needed restraint. The pulse rate was 160 and the temperature 104.5 F. The skin was hot, dry and dull red. The eyes were closed, but the eyeballs bulged. There was diffuse, symmetrical, rapidly pulsating goiter, having a thrill and bruit. The lungs were clear. The precordium was heaving; the heart rhythm was regular; gross murmurs were not present. The abdomen was normal; the bladder was distended. Two hundred and forty-five minims (15 cc.) of Lugol's solution were given by mouth during the first twenty-four hours; morphine was used to control restlessness; repeated ice packs rapidly reduced the temperature. Large quantities of orange juice, lactose and fluids were given. After four days of delirium, the patient gradually became more quiet and at the end of a week he was completely rational. He then exhibited exophthalmos goiter which still had a bruit, and slight tachycardia; there was little tremor. On the ninth day, the first metabolic rate determination was only + 19 per cent. The course and dosage of Lugol's solution is shown in chart 9.

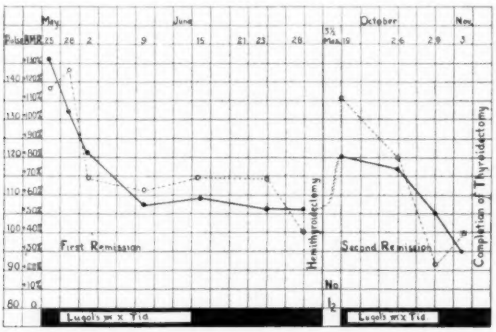

Chart 10.—Severe hyperthyroidism; beneficial use of iodine in two periods. Mr. G. E., severe exophthalmic goiter.

Apparently this young man had had mild hyperthyroidism, with an old colloid goiter; fifteen grains (0.9 Gm.) a day of potassium iodide produced marked complete remission to — 9 per cent. The iodine medication was then abruptly discontinued, and postiodine reaction begun, in which the disease reached maximum severity.

Lugol's solution can be given with benefit in the most severe cases of hyperthyroidism. The progress of the case illustrated in chart 10 is of interest. The first remission from + 132 per cent to + 55 per cent occurred in fourteen days. Because of operative difficulty, only hemithyroidectomy could be performed. The patient was wisely discharged without iodine, since even though the postiodine reaction would occur, a second remission before the final operation might then be obtained. This proved to be the case. On return, the metabolic rate had risen from + 52 per cent to + 80 per cent, but on administration of iodine,

it again fell to + 28 per cent, with a fall of pulse rate from 135 to 100. The pathologic report was, "Marked hyperplasia."

A patient who had exceptionally severe cardiac dysfunction reacted well to iodine, as indicated in chart 11. The gain in weight was not due to edema. The course of the disease in this patient was that of adenomatous goiter with hyperthyroidism. There was no definite time of onset. For years the patient had had dyspnea on exertion, and hypertension was marked. There was, however, a slight exophthalmos. Remission under Lugol's solution was complete. Pathologic report was, "Fetal adenomas with beginning differentiation."

To summarize: (*a*) Postoperative thyrotoxic crises do not occur when the administration of iodine is continuous during and for at least ten days after the operative period; (*b*) in severe crises, large doses of Lugol's solution are effective; (*c*) iodine has the usual action

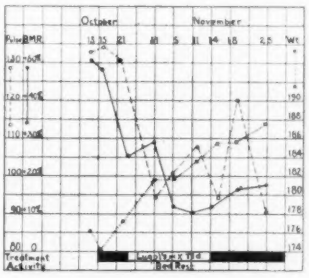

Chart 11.—Complete remission with excessive cardiac pathologic change. Mr. G. L., chronic hyperthyroidism; fibrillation, pathologic report: fetal adenoma, patient not operated on, died.

in hyperthyroidism, characterized by excessively high metabolic rate or by severe cardiac disease.

COMMENT

If it is true, as the clinical data offered indicate, that iodine does produce a temporary remission in all varieties of hyperthyroidism, a similarity of essential pathogenesis in all these varieties seems probable. Viewed in this light there is no qualitative difference between the mechanism producing hyperthyroidism in adenomatous goiter and that in exophthalmic goiter. The obvious clinical differences are only symptomatic, being dependent on difference in degree and in duration of hyperthyroidism.

Furthermore, if it were true that there was an essential difference between the various clinical types of hyperthyroidism, it might be expected that one of these would be resistant to iodine. The reverse is true. No single type of hyperthyroidism is alone resistant. Patients

with all the varieties of hyperthyroidism that I have observed have failed to give the iodine remission, from those with cases characterized by exophthalmos and hyperplasia to those with cases characterized by adenomatous goiter.

In relation to the induction of hyperthyroidism by iodine, it may be stated that in an examination of 125 patients with hyperthyroidism who had been given iodine, not a single instance of immediate increase in symptoms was found. On the other hand, under prolonged administration increasing symptoms were the rule, and postiodine reactions were common. One way in which iodine appears to induce hyperthyroidism is by suppressing temporarily an already present disease (remission), even though mild and associated with an adenomatous gland (6, chart 3); the gland then forces a return of the primary condition (recurrence) perhaps even in more severe form (4, chart 6). When the iodine is stopped, there is a rapid flourishing of the disease (postiodine reaction, chart 10).

From the experiments of Starr, Segall and Means [8] on thyroid feeding, and on injections of thyroxin by Sturgis [7] in relation to the site of action of iodine, it seems evident that the inhibiting action takes place in the thyroid gland and not in the general body tissues. This is further supported by the recent successive removals of thyroid tissue in patients with hyperthyroidism under iodine medication by Rienhoff.[8]

The deductions in regard to administration of iodine in hyperthyroidism, to be made from the clinical data illustrated, are as follows:

1. If operation is to be performed, iodine should be administered as described, for from ten to fourteen days, with the hope that a remission will occur.

2. If iodine medication is started, it should not be discontinued until the immediate effect of subtotal thyroidectomy is complete.[5]

3. If iodine has been administered for a long time before observation, (*a*) it should be continued in order to prevent the postiodine reaction; this is true even if iodine is held responsible for the existence of the present hyperthyroidism; or (*b*) the administration of iodine may be stopped, the postiodine reaction allowed to pass and iodine again given in the hope that a remission will then take place.

4. If a severe thyrotoxic crisis is present either before or after operation, relatively enormous doses of iodine are indicated.

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7. Sturgis, C. C.: Personal communication to the author.

8. Rienhoff, W. F., Jr.: Histological Changes Brought About in Cases of Exophthalmic Goiter by the Administration of Iodine, Bull. Johns Hopkins Hosp. **37**:285 (Nov.) 1925.

CONCLUSION

The course of hyperthyroidism under iodine medication is characterized by remission and recurrence during the administration of iodine and by a reaction, which may be extreme, after the iodine is discontinued; hence, the prolonged treatment of patients who have hyperthyroidism with iodine in dosage sufficient to produce these effects is without final benefit.

CARDIAC CHANGES SUBSEQUENT TO EXPERIMENTAL AORTIC LESIONS*

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In an attempted analysis of the complicated conditions found in organic heart disease in man, studies of experimental lesions in the laboratory animal are of recognized value. The great value of the experimental procedure is the production, at least initially, of a single restricted lesion, a knowledge of the date of its incidence and the possibility of subsequent unrestricted observation. Although a large amount of work has been done in studies of both the clinical condition occurring in man and the functional and anatomic sequences of experimental lesions, we are far from a satisfactory understanding or agreement in regard to certain of the most fundamental questions. Two of the more important of these considerations are the cause and progress of the hypertrophy of the cardiac muscle which accompanies most cases of organic heart disease and the alterations frequently observed in the electrocardiogram in clinical cases. The series of experiments described in this article was undertaken with the hope of adding to the knowledge concerning these two particulars.

SIZE OF HEART IN AORTIC STENOSIS AND REGURGITATION

Rosenbach [1] produced aortic regurgitation and, in a few instances, mitral regurgitation in rabbits and found evidence of dilatation and subsequent hypertrophy. The hearts were observed beating in situ, and measurements of the thickness of the ventricle were made and compared with those of normal controls. Müller [2] came to similar conclusions by comparisons of heart and body weight. Romberg and Hasenfeld [3] recorded a heart weight body weight ratio of 0.00219 in rabbits with aortic regurgitation as compared with 0.00195 in a series of controls. The left ventricle was the seat of the principal hypertrophy as determined by the comparative weights of the two ventricles. The right ven-

* From the Physiological Laboratory of the University of Wisconsin.

1. Rosenbach, O.: Artifizielle Herzklapenfehler, Arch. f. exper. Pathol. u. Pharmakol. **9**:1, 1878.

2. Müller, F.: Die Massenverhaltnisse des menschlichen Herzen, Hamburg and Leipzig, 1883.

3. Romberg, E., and Hasenfeld, A.: Ueber die Reservekraft des hypertophischen Herzmuskel, Arch. f. exper. Path. u. Pharmakol. **39**:332, 1897.

tricle was involved only in high grade insufficiency. Stadler [4] studied the hearts of four rabbits with aortic regurgitation, two with aortic stenosis and six with tricuspid regurgitation. The duration of the lesion varied from thirty to one hundred and seventy days. In each case, heart weight body weight ratios, weight of auricles, ventricular septum and each ventricle were given and compared with those of normal rabbits of the same body weight. In aortic stenosis and regurgitation the greatest increase in weight occurred in the left ventricle and septum, although some animals showed an increase in the right ventricle and auricle as well. In the animals with tricuspid regurgitation, the right ventricle was larger and the left ventricle definitely smaller than those of the controls. On histologic examination, evidences of hypertrophy in the former and of atrophy in the latter were found. Wolfer [5] obtained a heart weight body weight ratio of 0.00209 in a group of normal rabbits, and of 0.00275 in seven animals after aortic stenosis. All of the latter exceeded the normal average, and two, the normal maximum. The ratio between the weight of the left and the right ventricles was 1.7 in the normal series and 1.86 in the series of aortic stenosis. He also studied the hearts of seven animals with aortic regurgitation and found a heart weight body weight ratio of 0.0021 and left right ratio of 1.82. Schliephake [6] found only slight variations in the weight ratios in four rabbits with aortic regurgitation as compared with those of ten controls. Stewart [7] studied experimental aortic regurgitation in twenty dogs and compared weight ratios with twenty controls. Heart weight body weight ratio in the aortic regurgitation series was above the normal average in 90 per cent and above the normal maximum in 85 per cent. He found that the hypertrophy affected all chambers of the heart, although the left ventricle increased in absolute weight more than the other chambers. Hypertrophy developed with surprising rapidity, being evident within a week after the production of the lesion. Herrmann [8] more recently has published extensive series of measurements of heart weight in normal dogs and in dogs with experimental aortic regurgitation. He compared heart weight body weight ratios and the relative weights of the two ventricles to body weight and to each other. His principal results are summarized in table 3 and are compared with similar determinations made by us. In seventy dogs with aortic regurgitation, all but four

4. Stadler, E.: Experimentelle und histologische Beitrage zur Herzhypertrophie, Deutsches Arch. f. klin. Med. **91**:98, 1907.

5. Wolfer, P.: Experimentelle Studien zur Reservekraft des hypertrophischen Herzens, Arch. f. exper. Path. u. Pharmakol. **68**:435, 1912.

6. Schliephake, E.: Die veränderung des Ek nach künstlichen Aorten insuffizienz und Hypertrophie des linken Herzens, Ztschr. f. klin. Med. **97**:96, 1923.

7. Stewart, H. A.: An Experimental Contribution to the Study of Cardiac Hypertrophy, J. Exper. Med. **13**:187, 1911.

8. Herrmann, G. R.: Experimental Heart Disease, Am. Heart J. **1**:485, 1926.

exceeded the normal average heart weight body weight ratio established in 200 normal dogs, and fifty were above the upper normal range. In the relation of the weights of the two ventricles (left right ratio) there was evidence of preponderant hypertrophy of the left ventricle. All but five hearts exceeded the normal average ratio, while forty-three exceeded the upper normal range. In contrast to Stewart's [5] results, Herrmann did not find any evidence of hypertrophy in less than nineteen days. The maximum hypertrophy was obtained in approximately one hundred and ten days.

METHODS

In the present series of experiments the progress and extent of cardiac enlargement following experimental stenosis and regurgitation in dogs were studied by the determination of the area of the roentgen-ray silhouette of the heart taken at a distance of 1 meter from target to film and correcting for distortion. Extensive experience both in the experimental animal and in man has shown that the area of the frontal plane silhouette is the most accurate and reliable of the various possible measurements of the heart shadow. The dog's heart is suspended in the chest wall above the level of the diaphragm, and a clear outline, including the lower border is obtained, which makes the determinations of the area of greater accuracy in dogs than in man. Repeated observations in the same animal in this and preceding work in which this method was used have assured us of the remarkable constancy of the area of the cardiac silhouette in the same animal under the same conditions at different times. Such variations and errors in measurement fall well within a $\pm$ 5 per cent range. The roentgenographic method has the advantage that there is the possibility of numerous observations during the progress of the condition as compared with a single terminal observation when the weighing method is employed, and that a normal is determined in each animal rather than an average curve with variations established from a large number of animals. The method of comparative weight appears to have the inherent disadvantage of a wide range of normal variations, especially in dogs. This is true in a single series made on animals presumably derived from a restricted territory and measured by the same technic, and becomes greater when the standards established by different observers are compared. In Herrmann's extensive normal series, the heart weight body weight ratio and the left to right ventricle weight ratio vary through a $\pm$ 25 per cent variation and a $+$ 17 per cent to $-$ 25 per cent variation, respectively, from the average figures. According to this standard, it would be possible for a left ventricle, initially at the lower limit of normal, to increase 50 per cent of its original weight before passing the upper limit of normal, assuming that the right ventricle remained unchanged in weight. The principal disadvantages of the roentgen-ray method are that it does not distinguish between dilatation

and hypertrophy, and that it fails to show with accuracy which part of the heart is most affected. We have also made observations of the terminal weight in ten animals in the stenosis series and in eight in the regurgitation series.

The first series of experiments comprises nineteen dogs in which an aortic stenosis was produced by a constricting band. The third or fourth rib on the right side was resected under insufflation anesthesia, the pericardium opened and a band placed around the aorta immediately above the valves. The band was tightened until the vessel was obviously compressed and a distinct thrill developed on palpation. Metal bands of aluminum or German silver were used at first, but it was found that these had a tendency to erode the walls of the aorta, and elastic bands were employed subsequently. Ligatures of catgut were used in a few experiments but seemed to possess no advantage. Attempts were made to produce stenosis in twenty-eight animals. Two died from difficulties encountered in the operative procedure, one died from pneumonia on the ninth day following the operation and seven died within a period of from six hours to sixteen days following the operation, apparently as a result of too great a constriction of the vessel; autopsy, at least, failed to reveal any other cause of death. Eighteen animals recovered completely from the immediate effects of the operation and were observed for periods varying between twenty-eight and one hundred and forty-eight days. A roentgen-ray determination for the size of the heart and electrocardiograms of the three standard leads were made before and at varying periods subsequent to the operative procedure. In most cases two leads were recorded simultaneously to insure more accurate estimation of the electrical axis. At the end of the period of observation the animals were killed, autopsy was performed, the position of the band was noted and the presence of a constricted orifice was verified.

In fifteen dogs, experimental aortic regurgitation was produced by the introduction of a valvulotome through the right carotid artery. In all but two animals one valve leaflet alone was cut, in two (nos. 25 and 26) two valve leaflets were bisected. Roentgen-ray and electrocardiographic observations were made as in the stenosis series. The periods of observation varied from seventy to two hundred and ten days.

EXPERIMENTAL WORK

Experimental Aortic Stenosis.—So far as we know, the only previous experiments of a similar type in this lesion is the series of seven rabbits of Wolfer [5] and the two rabbits of Stadler [4] with observations for terminal weight. The roentgen-ray results for area and terminal weight in the present series of experiments are summarized in table 1. The figures following the column recording the day of observation give the area of the cardiac silhouette expressed in square centimeters. Exam-

TABLE 1.—*Aortic Stenosis*

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	Average
Before operation.....	36	47	49	42	40	38	35	41	48	38	60	30	49	48	38	47	42	45	43	
After operation.....	52	57	..	..	..	..	38	..	47	..	..	..	..	..	..	..	..	..	..	+18 %
4 days.....	55	..	49	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	
7 days.....	..	54	52	41	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	+ 6 %
10 days.....	62	51	..	..	40	..	..	..	..	..	..	..	..	..	..	..	..	..	..	
14 days.....	..	52	50	..	..	..	..	..	..	..	..	33	..	..	..	47	..	..	52	+ 8.8%
21 days.....	..	51	48	42	..	..	..	..	..	..	..	..	..	54	..	..	..	..	..	
28 days.....	..	57	52	42	..	..	..	..	..	38	..	..	53	51	..	..	47	45	51	+ 8.4%
35 days.....	..	56	50	41	41	39	..	..	..	..	..	28	..	51	38	51	..	..	..	
42 days.....	..	57	50	41	..	..	..	..	..	..	..	..	53	..	..	..	..	..	..	
49 days.....	..	58	49	41	..	..	44	45	..	..	..	..	53	..	..	..	..	..	..	+11 %
56 days.....	..	57	..	..	..	..	..	..	..	..	..	31	..	..	43	..	55	49	..	
63 days.....	..	..	..	..	..	..	..	..	..	..	58	..	..	..	..	..	..	..	52	
70 days.....	..	..	50	44	..	..	..	47	..	..	..	32	51	..	..	51	..	..	..	
77 days.....	..	56	49	42	..	..	..	..	..	..	..	..	..	50	..	..	55	..	..	
98 days.....	..	59	..	44	42	40	..	..	46	..	..	52	..	..	..	51	..	..	..	
106 days.....	..	..	51	47	..	..	..	..	..	..	..	..	..	..	..	..	..	52	51	
120 days.....	..	..	..	..	..	38	..	..	..	..	..	..	..	..	..	..	..	..	..	
134 days.....	..	..	51	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	
148 days.....	..	..	54	47	..	..	..	..	..	..	..	..	..	..	..	50	..	..	..	
Percentage change.....	..	+26	+10	+12	+5	0	+26	+15	−4	0	−3	+7	+4	+4	+13	+7	+31	+16	+18	+10.5
Body weight.....	..	8.62	9.50	8.40	8.66	8.34	5.2	9.2	11.2	7.76	6.9	6.42	11.84	11.4	8.54	10.5	11.0	11.6	11.7	
VW/BW*	..	810	715	668	..	..	..	772	..	..	..	571	505	519	602	621	622	..	..	642
LVW/BW*	..	550	425	447	..	..	..	576	..	..	..	317	318	334	364	390	334	..	..	401
L/R.....	..	2.17	1.60	1.86	..	..	..	2.01	..	..	..	1.27	1.71	1.82	1.53	1.78	1.16	..	..	1.69

* Decimal point and first two zeros omitted; 810 should read .00810.

ination of these data shows that there was little or no apparent change in cardiac size in five experiments, while a definite increase occurred in the remainder. The average for the whole group was an increase of 10.5 per cent of the original area. The greatest increase observed was 31 per cent. The final column of the table gives the average percentage increase above the normal at different periods subsequent to the operative procedure. These figures were obtained by determining the percentage change in each case recorded on the days noted and making an arithmetic average. A marked cardiac enlargement was noted in three of four animals observed immediately after the operative procedure. We believe this represents an initial dilatation from which the heart may partially or entirely recover before hypertrophy begins. It shows more

TABLE 2.—*Aortic Regurgitation*

Experiment	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	Aver.
Before operation	69	55	61	57	57	55	39	36	38	41	35	52	41	39	44	
After operation	70	65	67	60	53	52	44	38	..	..	..	..	..	..	..	+5.1
2 days	74	58	65	..	..	55	..	..	..	..	..	..	..	..	..	+2.1
7 days	66	54	..	62	56	55	44	..	..	..	..	..	..	..	..	+2.5
14 days	69	..	70	..	51	49	..	..	38	..	..	..	..	..	..	−1.4
21 days	..	54	73	57	54	46	..	..	..	45	..	..	..	..	..	+1.7
28 days	71	..	..	63	50	..	..	..	40	..	..	..	..	..	..	+2.5
35 days	69	62	70	59	51	47	..	..	..	..	..	..	..	..	..	+2.5
42 days	..	..	70	55	..	..	..	..	..	49	..	..	..	..	..	+8.9
49 days	75	65	..	55	..	..	..	..	..	..	..	..	..	..	..	+7.8
56 days	..	60	70	..	..	49	..	..	..	..	..	..	..	..	..	+8.9
63 days	75	..	73	..	55	..	..	..	..	56	..	..	..	..	..	+15.2
70 days	..	63	..	62	..	57	..	..	..	60	..	..	..	..	..	+18.3
77 days	75	59	76	..	61	..	..	..	..	..	..	..	..	..	..	.....
84 days	..	63	75	60	..	..	..	..	..	..	..	..	..	..	..	.....
98 days	80	69	80	..	..	..	..	..	..	..	48	57	43	39	51	+17.5
130 days	85	..	..	..	..	..	51	50	..	..	..	..	..	..	..	.....
180 days	..	..	..	..	64	60	..	..	..	..	..	..	..	..	..	.....
210 days	..	69	84	72	..	..	..	..	..	..	..	..	..	..	..	.....
Per cent change in area	+19	+25	+38	+26	+12	+9	+31	+39	+5	+46	+37	+10	+5	0	+16	+22
Body weight	14.4	12.7	14.2	11.9	13.2	9.0	9.06	8.9	..	..	..	..	..	..	..	.....
HW/BW	862	855	951	823	746	933	819	784	..	..	..	..	..	..	..	859
VW/BW	753	718	808	761	692	796	703	661	..	..	..	..	..	..	..	723
LVW/BW	402	408	517	445	352	461	403	412	..	..	..	..	..	..	..	425
L/R	1.17	1.32	1.77	1.40	1.41	1.31	1.34	1.60	..	..	..	..	..	..	..	1.41

clearly in the larger number of animals observed at this stage in the aortic regurgitation series. In one animal (exper. 1) continued dilatation occurred, and the animal died on the sixteenth day. The subsequent enlargement, to be interpreted probably as hypertrophy, develops slowly in most animals and appears to be usually complete at approximately the sixth week.

Experimental Aortic Regurgitation.—Data concerning roentgen-ray areas and observations for terminal weight in the aortic regurgitation series are presented in table 2. Previous roentgen-ray studies in this condition are those of Sands,[9] Bazett [10] and Herrmann.[8] Sands employed

9. Sands, J.: Chronic Aortic Regurgitation in Dogs, xi Int. Physiol. Congress, Quart. J. Exper. Physiol., suppl. vol., 1923, p. 215.

10. Bazett, H. C.: Further Observations on Experimental Aortic Regurgitation, Proc. Am. Physiol. Soc., Am. J. Physiol. **72**:201, 1925.

short exposures (from one to ten seconds) in which the incidence in the heart cycle and the relation to the phase of respiration were determined by simultaneous electrocardiograph and respiratory records. Immediately after and for a period up to two weeks following the lesion, the hearts were longer and narrower. Later the hearts were larger in all dimensions. Bazett found that considerable hypertrophy occurs but develops slowly. Herrmann noted that many of his animals with aortic regurgitation showed evidences of cardiac enlargement on roentgen-ray examination, but he does not present any data. The average percentage changes from the normal at different times are given in the last column of the table and charted in figure 1. Six of eight dogs showed an enlarged heart immediately following the injury to the valves. In two of the four in which this was observed, the initial enlargements disappeared within seven days, in one by the twenty-first day, and in one it apparently

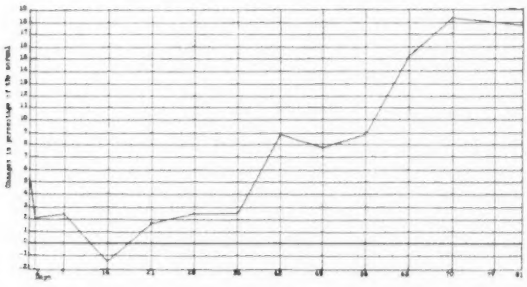

Fig. 1.—Average changes in size of heart in aortic regurgitation.

remained. It seemed possible that heart rate changes following the operative procedure might be of importance in this connection. Meek [11] has shown that the size of the dog's heart is little affected by moderate changes in rate, but that it rapidly decreases in size with a fast rate. In the six hearts showing initial enlargement (19, 20, 21, 22, 25 and 26) heart rate was higher after operation (average percentage increase of 67 per cent) than before in four (19, 20, 23, 25), unchanged in one (21) and slightly decreased in one (22). The greatest initial enlargement observed (exper. 20) was associated with a 33 per cent increase in heart rate. In the two hearts failing to show initial enlargement (23 and 24), the heart rate increased in the former 51 per cent, and in the latter it decreased 17 per cent as compared with the rate before operation. It seems difficult to associate any change in cardiac area observed with changes in heart rate. From the average figures it appears that a second period of enlargement follows the first after approximately two weeks,

11. Meek, W. J.: Effect of Changes in Pulse Rate on Diastolic Heart Size, Am. J. Physiol. **70**:385, 1924.

and continues at first rapidly and then more slowly to beyond the hundredth day. The most probable explanation of the results is that the initial enlargement is an initial cardiac dilatation. Later the ventricles in most cases appear to regain their normal tonus, and this is succeeded by enlargement caused by hypertrophy.

The Electrocardiogram in Experimental Aortic Stenosis and Regurgitation.—Fraser [12] recorded the electrocardiogram during dilatation in rabbits' hearts produced by the injection of spartein and epinephrine hydrochloride. Dilatation of the right side of the heart as determined by roentgen-ray observations, produced increase of the R and decrease of the S wave. Dilatation of the left side produced opposite effects. When both sides were dilated, no change was observed. Schliephake [6] recorded lead II from four rabbits with experimental aortic regurgitation. Q and R increased, especially the former. The T wave at first decreased and then increased as the hypertrophy developed. Sands [9] found that preponderance in the left ventricle was not present even after full hypertrophy developed as a result of aortic regurgitation. Bazett recorded an increase in Q and R waves and a reduction or disappearance of the S wave in all leads, while the duration of the QRS group was increased. Herrmann [8] stated that in the electrocardiogram only one of the seventy dogs with aortic regurgitation in his series showed any significant changes (left preponderance). This occurred in the dog showing the greatest relative hypertrophy of the series.

In clinical aortic regurgitation preponderance of the left ventricle occurs more frequently than in the normal heart. In twenty-one cases of aortic regurgitation with no history or present indications of incompetence, preponderance of the left ventricle was noted in 53 per cent as compared with 24 per cent in a series of 100 clinically normal hearts. It is interesting to know whether this tendency to axis deviation is an early or late change in the progress of the hypertrophy. It is also important to determine by detailed studies of frequent electrocardiograms whether or not any changes occur which are characteristic of early dilatation or hypertrophy.

Electrocardiograms were made by the standard three leads in all animals in both the stenosis and regurgitant series whenever roentgen-ray observations were made. In most cases two leads were recorded simultaneously to insure greater accuracy in measuring the electrical angle. These curves have been further analyzed respecting possible changes in heart rate, PR, QRS and RT intervals and Q, S and T waves in the different leads. The relationship between changes in rate and changes in PR interval were inconstant and apparently were not

12. Fraser, F. R.: Changes in the Electrocardiogram Accompanying Experimental Changes in Rabbits' Hearts, J. Exper. Med. **22**:292, 1915.

significant. The QRS interval was unchanged or slightly decreased in 66 per cent; increased in the remainder. The former showed an average terminal cardiac area of + 14 per cent, as compared with + 6 per cent in the latter. It is well known that in clinical hypertrophy the QRS interval is frequently increased, especially in the presence of left axis deviation. Our results would indicate that this is not a change characteristic of early hypertrophy. The RT interval, as an approximate measure of ventricular systole, is of interest. It was definitely increased in 55 per cent, and unchanged or slightly decreased in the remainder. Terminal cardiac area was increased, 11 per cent in the former group, 14 per cent in the latter. There thus does not seem to be an association between the length of systole, as thus estimated, and the extent of hypertrophy. The electrical axis was within its normal range at the initial observation in all experiments in both series except in one instance. The animal in experiment 32 showed a deviation of the right axis of — 178 degrees, practically unchanged at the terminal observation in this animal. Deviation of the axis seems to be rare in normal dogs as compared with human beings. The average normal angle was + 64 in the stenosis series and + 58 in the regurgitation series. The range in the two series (excluding the one case of right axis deviation) was from + 37 to + 82. The average angle in the stenosis series showed a tendency to shift to the left (from + 64 to + 47) at the terminal observations, but practically no change occurred in the series of aortic regurgitation. Changes in the Q, S and T waves in the three leads were inconstant and apparently without significance. In the stenosis series the sum of the Q waves in the three leads increased in 45 per cent and decreased in 45 per cent. The S waves increased in 33 per cent and decreased in 45 per cent. The duration and size of the T wave in the different leads in normal dogs is extremely variable and inconstant. T^1 and T^2, as well as T^3 negativity are common, and changes occur from time to time in the same animal without apparent cause. The T wave in the dog fails to have the clinical significance which it appears to have in man. Equally inconstant and insignificant changes occurred in the animals with experimental stenosis and regurgitation.

The degree of cardiac dilatation and hypertrophy encountered in dogs as a result of experimental aortic lesions thus fails to produce any significant change in the electrocardiogram. In order to determine whether or not extreme grades of dilatation in an otherwise normal heart showed any important changes, five additional experiments were performed. In four dogs, acute and massive dilatation of the left ventricle was produced by transient occlusion of the descending thoracic aorta, and in one dog similar transient dilatation of the right ventricle was secured by the rapid infusion (200 cc. within ten seconds) of physiologic sodium chloride at body temperature through a large cannula

into the jugular vein under a pressure of about 80 millimeters of mercury. In the former experiments, the aortic ligature was laid after resection of the rib, and the thorax was closed and normal respiration reestablished before the experimental procedures were performed. Electrocardiograms from the three leads were made in two experiments by three galvanometers recording simultaneously. In the three other experiments, two leads only were recorded. Carotid blood pressure was also recorded. The changes in the electrocardiogram resulting from aortic occlusion with dilatation of the left ventricle or rapid venous infusion with dilatation of the right ventricle were practically negligible. The only effect observed was a slight transient increase in PR and RT intervals. Figure 2 is the electrocardiogram made during a period of aortic occlusion. In two dogs, the same procedure was carried out after the production of an aortic regurgitation, with identical results.

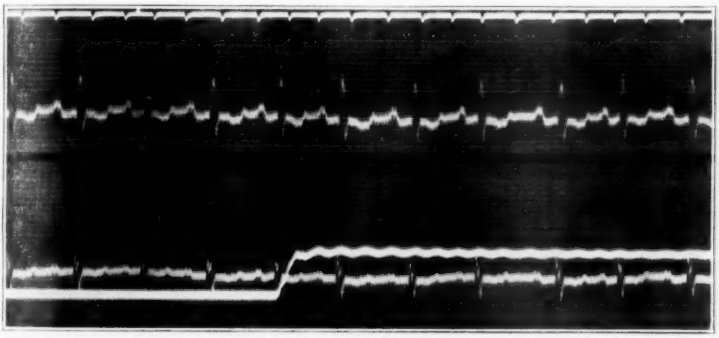

Fig. 2.—The electrocardiograms (lead 2 upper, and lead 3 lower curve) during temporary occlusion of the descending aorta in a dog. Onset of occlusion marked by rise of marking pen; time in one-fifth of a second intervals.

Terminal Heart Weight Determinations in Stenosis and Regurgitation.—Determinations of heart weight from ten experiments in aortic stenosis and eight experiments in aortic regurgitation are given in tables 1 and 2. We have, in addition, made similar determinations on seventeen normal animals, and while this series is small compared to Herrmann's data, it represents a normal established under the same conditions and with the same technic as that of the abnormal animals. The technic of separating and weighing the two ventricles was essentially that of Herrmann's. Comparisons of the normal animals with the more important measurements in aortic stenosis and regurgitation are given in table 3. It will be noted that our figures are in most cases lower than those of Herrmann, both for the normal and for the abnormal series, and that less striking differences are established. Probably the two most

important measurements are the ratio of body weight to the weight of the left ventricle (LVW/BW) and the relative weights of the two ventricles (R/L). In the former case, the averages of the two abnormal series exceed the averages of both normal series, but are definitely lower than that of Herrmann's series of aortic regurgitation. In the eighteen animals with stenosis or regurgitation, all exceeded our average normal figure, and twelve exceeded Herrmann's normal average. The right left ratio in our series, however, fails to indicate preponderant hypertrophy of the left ventricle.

THE DYNAMICS OF AORTIC REGURGITATION AND THE RESERVE FORCE OF THE HYPERTROPHIED HEART

The usual interpretation of the dynamics of insufficiency of the aortic valves is a regurgitation of blood during diastole with a larger amount of blood and an increased tension in the left ventricle at the end of diastole

TABLE 3.—*Determinations of Heart Weight*

	Heart Weight, Body Weight		Ventricle Weight, Body Weight		Left Ventricle Weight, Body Weight		Right Ventricle Weight, Left Ventricle Weight	
	Average	Maximum	Average	Maximum	Average	Maximum	Average	Maximum
Herrmann's normal	798	934	635	872	369	472	1.40	1.72
Present normal	.....	.....	516	630	314	388	1.63	1.79
Aortic stenosis	.....	.....	642	810	401	550	1.69	2.17
Herrmann's series of aortic regurgitation..	1,053	1,388	849	1,233	554	814	2.00	3.00
Present series of aortic regurgitation	859	933	723	808	425	517	1.41	1.77

The decimal point and one or two zeros have been omitted except in the figures of the last two columns. Thus 798 should read 0.00798 and 1,053 should read 0.01053.

and an increased contraction of the muscle with an increased outflow during systole. In the light of the modern conception of cardiac activity, the increased contraction is the direct result of the increased initial load on the tension or length of the muscle fiber. Stewart [13] has dissented from this view on experimental grounds. By the use of the ventricular plethysmograph in dogs he found the output practically unchanged as a result of the production of aortic insufficiency, and concluded that the regurgitation of blood was negligible, amounting at the most to a fraction of a cubic centimeter. The hypertrophy of the left ventricle was explained on increased diastolic tension caused by transmission of aortic pressure. This view has also been supported by Zollinger [14] from results from similar experiments, in which the pericardium was used as

13. Stewart, H. A.: Experimental and Clinical Investigation of the Pulse and Blood Pressure Changes in Aortic Insufficiency, Arch. Int. Med. **1**:102 (Jan.) 1908.

14. Zollinger, F.: Zur experimentelle Pathologie und Therapie der akuten Aorten insufficienz, Arch. f. exper. Path. u. Pharmakol. **61**:193, 1909.

a plethysmograph, although he found evidence of increased diastolic filling. MacCallum,[15] however, employing a heart-lung preparation in which both the output from the aorta and the output from the ventricle were measured and compared, found that regurgitation plays a prominent part in aortic insufficiency and is sufficient to account for the hypertrophy. Wiggers [16] came to essentially the same conclusion from intracardiac pressure measurements and concluded that the increased output is due to an increased and longer systole. We have measured the cardiac output by means of a cardiometer in three experiments on dogs before and after the production of an aortic regurgitation. In each case the injury to the valve caused a significant increase in output associated with a greater diastolic relaxation. The immediate increase in output per beat was 20 per cent, 11.5 per cent and 30 per cent, respectively; an average of 20.5 per cent in the three experiments. In order to test the comparative ability of the ventricle to meet a marked increase in load after injury of the aortic valve, measurement of the output during transient aortic compression was made in these experiments. In the normal heart, transient occlusion of the descending thoracic aorta causes a decrease in cardiac output associated with the marked rise of aortic pressure central to the point occluded. This fall in output is greater in the presence of an incompetent aortic valve than with the intact heart. In the three experiments, an average of several trials in each case gave a decreased output per beat as a result of aortic occlusion of 16 per cent, 31 per cent and 13 per cent before and of 50 per cent, 54 per cent and 18 per cent after the production of aortic regurgitation. The corresponding percentage reductions for minute volume were 17 per cent, 35 per cent and 13 per cent before and 62 per cent, 53 per cent and 18 per cent after. It appears, therefore, that the reserve force of the normal cardiac muscle is exceeded when an overload of this extent is applied to a heart with a defective aortic valve. It would seem that the effect of hypertrophy is, at least in part, to add to this reserve and to enable the heart with a valve lesion to meet an overload of considerable magnitude. Romberg and Hasenfeld [3] studied the reaction of normal rabbits and compared it with the reaction of rabbits with hypertrophic hearts from aortic regurgitation or stenosis or from injection of spartein and epinephrine hydrochloride, to short periods of asphyxia, sensory stimulation, abdominal massage and clamping the thoracic aorta. Although marked differences were noted between different animals, these authors believed that the evidence they obtained pointed to the conclusion that the development of hypertrophy increases the reserve force of the heart

15. MacCullum, W. G.: The Changes in the Circulation in Aortic Insufficiency, Bull. Johns Hopkins Hosp. **22**:197, 1911.

16. Wiggers, C. J.: The Dynamics of Aortic Insufficiency, Arch. Int. Med. **16**:132 (July) 1915.

with an experimental lesion until it is approximately equal to the normal heart. The same conclusion was obtained by Wolfer [5] in whose work the extent and duration of the rise of arterial pressure on clamping the aorta in thirteen normal rabbits was compared with twenty-five rabbits with hypertrophic hearts subsequent to aortic stenosis, aortic regurgitation and administration of epinephrine hydrochloride. According to Eppinger and Knaffl,[17] starvation for several days preceding this test of cardiac reserve reduces the reserve in the normal heart, and reduces it to a greater extent in the hypertrophic heart resulting from aortic regurgitation. It would seem, therefore, that while hypertrophy increases the reserve and the ability of the muscle to meet an increased total amount of work, the hypertrophic muscle is more susceptible to disturbances of its nutrition than the normal muscle.

MYOCARDIAL CHANGES IN CARDIAC HYPERTROPHY

Two divergent views regarding the nature of the process in hypertrophy of cardiac muscle are found in the literature. The more prevalent one is that the process is primarily a work hypertrophy stimulated by mechanical conditions of load. The other view is that hypertrophy is the result of a progressive inflammatory process caused by a pathologic nutritive stimulus. The latter view has been supported particularly by Albrecht [18] on the basis of observations made on human hearts. The reports derived from the study of experimental hypertrophy, on the other hand, incline to the former view. Tangl [19] compared the cross diameter of the muscle cells in the hearts of normal rabbits of different body weights and in hypertrophic hearts resulting from experimental aortic regurgitation. He found that the diameter of the fiber increased from 5.57 to 15.33 microns with body weight from 610 to 2,600 Gm., while in hypertrophic hearts a similar relationship existed in which the range in cross diameter was from 14.24 to 20.17 microns. He therefore compares hypertrophy with physiologic growth of the muscle. Most workers believe that the hypertrophy as well as the normal growth of the heart is due to enlargement of the individual fiber, and that mitosis does not occur. This enlargement is ascribed to increase of the fibrillae by some observers, to the sarcoplasm by others. With the increase in the size of the fibers, several observers have noted a frequent but apparently not invariable increase in connective tissue. Stadler [4] ascribes the increase of connective tissue to the mechanical stimulus of dilatation and the increase in size of the fiber to the mechanical stimulus of increased

17. Eppinger, H., and Knaffl, E.: Ueber Herzinsufficienz, Ztschr. exper. Path. u. Therap. **5**:77, 1909.

18. Albrecht, E.: Die Herzmuskel und seine Bedeutung für Physiologie, Berlin, 1903.

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work. Eight of the hearts from our series of aortic regurgitation have been examined for us by Dr. E. M. Medlar of the Department of Pathology of the University of Wisconsin. All showed a definite enlargement of the fibers of the left ventricle and septum. The outer wall of the right ventricle usually showed some hypertrophic cells, but less marked and less extensive than in the left ventricle. There was no evidence of degenerative changes in the heart muscle nor of increase of fibrous tissue in any instance.

CONCLUSIONS

1. Experimental aortic stenosis and insufficiency in dogs is usually associated with a gradually developing cardiac hypertrophy.

2. This hypertrophy is preceded by a stage of initial dilatation, usually passing off in part or completely within a few days.

3. Aortic insufficiency is associated with regurgitation of blood into the left ventricle and an increased diastolic widening of this chamber.

4. The heart with aortic insufficiency before hypertrophy develops fails to react as effectively to an overload as does the normal heart.

5. There are no electrocardiographic changes characteristic of the early dilatation or hypertrophy subsequent to aortic lesions. Even extreme degrees of dilatation in the normal heart fail to cause significant changes in the electrocardiogram.

6. The histologic changes following aortic regurgitation are those characteristic of simple hypertrophy without evidence of degenerative processes in the cardiac muscle.

We have known that Dr. H. C. Bazett of the University of Pennsylvania was carrying on a series of observations closely paralleling our own. Through the courtesy of Dr. Bazett there has been an interchange of manuscripts, and we wish to express our appreciation of this. The principal difference in our conclusions appears to be the question of the occurrence of an early enlargement subsequent to aortic regurgitation. We are unable to suggest the reason for this difference in experimental results, and it would appear that further work on this important question is desirable. We should also like to thank Dr. E. M. Medlar of the Department of Pathology of the University of Wisconsin for making the histologic examinations for us.

CHRONIC ACIDOSIS IN RABBITS AND IN DOGS

WITH RELATION TO KIDNEY PATHOLOGIC CHANGE *

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Change in the ability of the kidney to eliminate acids has been recognized as one of the fairly constant symptoms of renal disease. Palmer and Henderson [1] report an abnormally high acidity of the urine caused by a decrease of urinary ammonia in patients with nephritis usually of the glomerular type. The same investigators,[2] also Sellards,[3] Hösslin,[4] and Peabody,[5] find that the amount of alkali which must be ingested before the urine becomes alkaline is increased in nephritis. Sellards reports that this is particularly true in interstitial renal injury. Austin and Cullen [6] review the literature and draw the conclusion that nephritis gives rise to a disturbance of the acid base equilibrium, and that it may lower both the alkali reserve and the plasma p_H.

These investigators and many others, while recognizing the constant appearance of a disturbed acid excretion, have supposed that this was a consequence of the renal damage. Fischer,[7] on the other hand, believes that acid elimination may play an etiologic rôle in nephropathologic change. He supports his theory by experiments in which he injects acid intravenously in rabbits and finds albumin and casts in the specimens of urine in a few hours. Other work of this nature has been reported as far back as 1878, when Kobert [8] found that 5 per cent phosphoric acid given to dogs and rabbits either by stomach tube or by intravenous injections resulted in albumin, casts and even blood in the urine.

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* From the Department of Pathology, Harvard University Medical School.

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6. Austin, J. H., and Cullen, G. E.: Hydrogen Ion Concentration of the Blood in Health and Disease, Medicine **4**:275 (Aug.) 1925.

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Ewing [9] obtained albumin and hyaline casts in fifty-two hours in a rabbit that had received 2.16 Gm. hydrochloric acid subcutaneously. Microscopically, he found granular and hydropic degeneration of the renal tubule cells. MacNider [10] conducted a series of four hour experiments in which dogs received two doses of two-tenths normal hydrochloric acid, 5 cc. per kilogram. Albumin and casts appeared in the urine. Microscopically, the kidneys showed injury to the convoluted tubules, advanced cloudy swelling, granules in the cytoplasm and irregularly staining nuclei. Goto [11] observed that acid (from 0.5 per cent hydrochloric acid to 1 cc. per kilogram) administered by mouth to two dogs produced an "acute nephritis."

Acid has been used in these experiments in relatively large quantities over a short period of time, and the effect has been similar to that produced by other more toxic chemicals. Acute tubular injury has resulted.

PLAN OF EXPERIMENTS

The experiments described in this paper were planned to determine whether a mild chronic acidosis, or a lowering of the plasma carbon dioxide capacity, extending over a long period of time, would result in kidney damage.

The acidosis was produced by administering by stomach tube one-tenth normal hydrochloric acid or one of the hydrochloric acid forming substances, ammonium chloride or calcium chloride, to rabbits and dogs. The dosage of acid-forming substances was so regulated that the carbon dioxide capacity of the plasma became and remained slightly below normal over periods of months. It was difficult to regulate this dosage for rabbits. They often contracted a severe acidosis. Specimens of urine were examined at regular intervals for albumin, the p_H was determined and the sediment was examined microscopically.

ACIDOSIS IN RABBITS, MATERIAL AND METHODS

Fifteen young animals weighing approximately 2 Kg. were used. Six of these were kept as controls. All animals were maintained under the same living conditions, on a diet of oats and various greens and water as desired. For spontaneous ear infection with B. necrophorus, which made its appearance in a few animals, these animals were treated by pouring ether into the ear every other day until the infection disappeared completely.

9. Ewing, James: Acidosis and Associated Conditions, Arch. Int. Med. **2**:330 (Nov.) 1908.

10. MacNider, W. deB.: Studies Concerning the Influence of a Disturbance in the Acid-Base Equilibrium of the Blood on Renal Function and Pathology: Study I. The Effect of Acid and Alkaline Solutions on Renal Function and Pathology in Normal Dogs, J. Metabolic Research **3**:511 (April) 1923.

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Weekly examinations of the urine were made on urine freshly obtained by pressure on the bladder. In order to make certain that the bladder should contain a sufficient volume of urine, the animals were put into rat cages for three or four hours previous to taking the specimen of urine. They were sufficiently crowded and uncomfortable in these small cages so that they did not urinate during that period. The p_H of the urine was determined colorimetrically with the LaMotte standards on all specimens of urine acid to litmus. Albumin was determined by heat and acetic acid. Acid was also added to urine which was cold, as it was found that frequently a precipitate formed under these conditions. Albumin as reported refers to the density of the cloud in the heated specimen after that in the cold urine has been subtracted. It is reported as a faint trace, trace, one plus, two plus or three plus. Microscopic examination of the sediment obtained by centrifugalization was made promptly.

Blood for plasma carbon dioxide capacity was drawn at weekly or bi-weekly intervals as the condition of the animal warranted. The specimen was collected by inducing hyperemia in the ear with ether, cutting the marginal vein and allowing the blood to fall into an oxylated tube. After gently mixing with a rod, oil was poured on the surface, and the blood was centrifugalized. This is not an accurate way of collecting blood for gas analysis. The method was checked, however, by drawing simultaneous specimens from the heart. The difference of about 3 per cent by volume was of no practical importance in these experiments. A rabbit's plasma carbon dioxide capacity has normal limits as wide as 45-70 per cent by volume. The method of analyzing the blood was that described by Van Slyke.[12] The analyses of the last six months were made on the constant volume Van Slyke machine.[13]

Nine of the rabbits received tenth normal hydrochloric acid, calcium chloride or ammonium chloride by stomach tube over periods of time which varied from ten days to one year. The time and dosage, together with urine, blood and postmortem observations, are given in tables 1 and 2.

The use of tenth normal hydrochloric acid as a means of lowering the reserve alkali of the blood needs no explanation. Ammonium chloride and calcium chloride increase the chloride anions of the blood, because in the case of ammonium chloride, the ammonia is probably converted into neutral urea, while in the case of calcium chloride, a large portion at least of the calcium is eliminated in the stool, while the chlorine ion is absorbed. Either substance, therefore, increases the hydrochloric acid metabolism of the body. Haldane[14] has reported the production of acidosis in himself both after the ingestion of calcium chloride and ammonium chloride. Gambler, Ross, and Tisdall[15] and Gamble and Ross[16] administered calcium chloride, ammonium chloride, and hydrochloric acid in the treatment of tetany and proved that calcium chloride

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13. Van Slyke, D. D., and Neill, J. M.: The Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, J. Biol. Chem. **61**:523 (Sept.) 1924.

14. Haldane, J. B. S.; Hill, R., and Luck, J. M.: Calcium Chloride Acidosis, J. Physiol. **57**:301 (June) 1923. Haldane, Priestley, Baird and Douglas: Ammonium Chloride Acidosis, J. Physiol. Proceedings **57**:11 (Feb.) 1923. Haldane, J. B. S.: Experimental and Therapeutic Alteration of Human Tissue Alkalinity, Lancet **1**:537 (March 15) 1924.

15. Gamble, J. L.; Ross, G. S., and Tisdall, F. F.: Studies in Tetany: Effect of Calcium Chloride Ingestion on the Acid-Base Metabolism of Infants, Am. J. Dis. Child. **25**:445 (June) 1923.

16. Gamble, J. L., and Ross, G. S.: Studies in Tetany: The Effect of Hydrochloric Acid Producing Substances on the Acid-Base Metabolism of an Infant, Am. J. Dis. Child. **25**:470 (June) 1923.

and ammonium chloride as well as hydrochloric acid lowered the plasma bicarbonate. Hydrochloric acid and presumably the other substance also lowered the p_H of the plasma. They found that only about 40 per cent of the calcium chloride ingested acts as hydrochloric acid, while probably all of the ammonium chloride ingested exerts an acid effect. One gram of ammonium chloride, which contains approximately 0.66 Gm. chlorine, would be equivalent to 180 cc. tenth normal hydrochloric acid. One gram of calcium chloride, if all the calcium were eliminated via the stool, and all the chlorine absorbed, would be equivalent to approximately the same, 180 cc. tenth normal hydrochloric acid.

Because of the possibility that ammonium chloride administered over a long period of time might introduce extraneous effects caused by ammonia and not by acid, three of the rabbits received tenth normal hydrochloride acid over long intervals of time during the experiments. There was no difference in the results. Calcium chloride was given to the rabbits during a large part of the experimental period. Tenth normal hydrochloric acid was finally stopped because such large volumes of fluid were necessary. The ammonium chloride and calcium chloride were given in 2 per cent solution.

The animals, with the exceptions noted in the tables, were killed, and autopsy was performed immediately. Sections were fixed in Zenker's solution and were stained with hematoxylin and eosin stain or by Giemsa's method.

EXPERIMENTAL OBSERVATIONS ON RABBITS

The individual variations in dosage and in the response of the animal to the acid make it impracticable to average the figures and present the data in a single table. The animals will be described as a single group during the first few days. They will then be divided into two groups: animals that never had a severe acidosis, that is a plasma carbon dioxide combining power below 30 per cent by volume, and the animals that developed a severe acidosis. Tables 1 and 2 contain the data for these two groups.

Previous to giving the acid, the specimens of urine of the nine animals used in the experiment were alkaline, there were no casts in the sediment, and eight of the nine had no albumin. One showed a faint trace. The plasma carbon dioxide capacity varied between the limits of 46 per cent by volume and 70 per cent by volume. These observations were made over a control period of one month.

The administration of from 5 to 7 Gm. of ammonium chloride to four animals over a period of three days to one week resulted in the appearance of albumin in the urine, which was a faint trace in one animal but a one plus amount in the others. The specimens of urine became acid; the p_H dropped as low as 5.4. Casts had appeared in the urine of one animal. After 7 Gm. of calcium chloride given over the period of a week to one animal, the albumin test gave a plus two reaction. The administration of from 100 to 350 cc. of tenth normal hydrochloric acid, given to four rabbits over a similar period of time, produced an acid urine, and in all but one case albumin varying from a faint trace to one plus. In all these animals the plasma carbon dioxide capacity was unchanged.

At the end of the first few days, without changing the reserve alkali of the body, the animals had been forced to excrete an acid urine and in all but one case varying amounts of albumin, while one rabbit had showed casts. It soon became evident, however, that the rabbit that does not produce ammonia to neutralize the acid eliminated in the course of

TABLE 1.—*Severe Acidosis*

Rabbit	Duration of Experimental Period	Dosage of Drugs Administered	Urine Observations: Average p_H	Urine Observations: Average Albumin	Urine Observations: Casts	Carbon Dioxide per Cent by Volume: Average	Carbon Dioxide per Cent by Volume: Lowest	Hours Postmortem Cause of Death	Microscopic Kidney Observations
4	11 days	16.2 Gm. NH_4Cl	6.4	+	Hyaline, granular	39	12	0 Killed	Epithelium of convoluted tubules, swollen, vacuolated, completely filling lumen; nuclei showed karyolysis; slight spontaneous nephritis
7	18 days	18.6 Gm. NH_4Cl, 8.0 Gm. $NaHCO_3$	4.9	++	Hyaline, granular	37 61*	20	0 Acidosis	No swelling of tubular epithelium; nuclei filled with many deep purple punctate dots of chromatin; numerous casts in tubules; no spontaneous nephritis
11	36 days	26.8 Gm. NH_4Cl	5.2	+	All types terminally	45	15	Biopsy	Tubular epithelium swollen, vacuolated; both pyknosis and karyolysis of nuclei; slight spontaneous nephritis
	3 weeks	.....	7.0	++	All types terminally	15	..	0 Killed	Tubular epithelium in places showed regeneration; many epithelial cells with no cytoplasm, and pyknotic nuclei; pyknosis much more extensive; numerous casts in tubules
14	8.5 mo.	5,510 cc. N/10 HCl, 45.0 Gm. NH_4Cl	5.4	++	Granular, occasionally all types	50	11	Biopsy†	Some cellular débris and casts in tubules; slight spontaneous nephritis; essentially normal
	7.5 wk.	22.0 Gm. NH_4Cl	5.0	++	All types	47	14	0 Killed	Slight swelling of convoluted tubular epithelium; some nuclei of epithelial cells pyknotic; slight spontaneous nephritis
6	11 mo.	166.0 Gm. NH_4Cl	5.0	++	All types	35	18	Biopsy	Tubular epithelium swollen, vacuolated; many nuclei pyknotic; no spontaneous nephritis
	3 weeks	.....	...	..	.....	..	..	0 Killed	Condition practically unaltered, slightly improved

* Per cent by volume of carbon dioxide at time of death.
† No acidosis at time this kidney was removed.

metabolism rapidly acquires a severe acidosis. Two of the animals were killed by the acidosis, one in eleven days and one in eighteen days, before this fact was fully appreciated. Even with careful watching subsequent animals were thrown into periods of severe acidosis from which they recovered.

The group of nine animals, therefore, is divided into two groups, one group consisting of rabbits 15, 16, 17 and 18, that at no time had a plasma carbon dioxide capacity below 30 per cent by volume. Animals 4, 6, 7, 11 and 14 had severe acidosis one or more times.

Table 1 summarizes the procedures and results in the group that had severe acidosis. Grossly and microscopically, the pathologic observations were uniform. The kidneys, grossly, were moderately swollen and pale. When spontaneous nephritis, so characteristic of rabbits, was present, it was recognized by small diffuse pits on the surface. On section, the proportion of cortex to medulla was normal. Extreme paleness was the outstanding feature.

Microscopically, with Giemsa's stain, the epithelium of the convoluted tubules was undergoing acute degeneration. The cells were so swollen as to fill the lumen completely; the cytoplasm was granular and vacuolated, the nuclei were usually deep violet, shrunken and irregular in contour, although rabbits 4 and 11, under treatment a short time, showed swollen, pale nuclei also. There were casts in the collecting tubules and a finely granular precipitate in some of the glomerular spaces. The glomeruli were normal. The observations were the same irrespective of the duration of the experiment. There was no intertubular proliferation of cells. Although the kidneys of these animals had been subjected to prolonged irritation, which was sufficient to cause the constant appearance of albumin and casts in the urine, no indication of a chronic response on the part of the tissues was obtained. The picture was that of a mild acute injury to the tubular epithelium and was essentially that of cloudy swelling.

Animals 4 and 7 are interesting in that they both received approximately the same amount of ammonium chloride and both were killed because they were in a moribund condition caused by acidosis. Rabbit 7, fig. 2, however, had received 8 Gm. of sodium bicarbonate during a period of two days previous to his death. His plasma carbon dioxide had returned to normal. With the exception of the great number of casts in the tubules and a slight degree of pyknosis of the nuclei, his kidneys were not microscopically abnormal, while those of rabbit 4, fig. 1, showed the tubular degeneration described in the foregoing. The nuclei were swollen and pale, or pyknotic.

Rabbit 11 was operated on in the stage of severe acidosis, and a portion of the right kidney was removed. This showed microscopically the characteristic picture of tubular degeneration. The kidney became infected postoperatively. Leukocytes and bacteria appeared in the urine, and the animal was killed seven days after the operation. In addition to the local area of infection in the right kidney, an early thrombus was found microscopically on the mitral valve. Besides the tubular degeneration in the kidneys, there often were adhesions between the glomerular

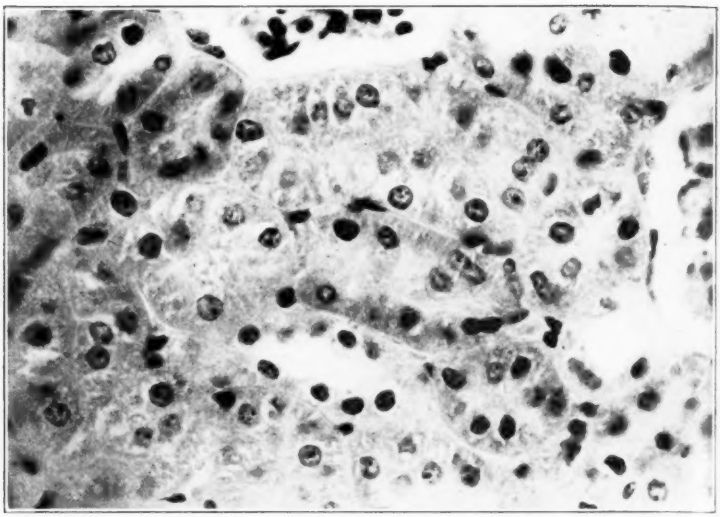

Fig. 1.—Convoluted tubules from the kidney of rabbit 4. The animal had received 16.2 Gm. of ammonium chloride over a period of two days. The plasma carbon dioxide had fallen to 12 per cent by volume. The combination of swollen cytoplasm with nuclei which are either swollen and pale or pyknotic is characteristic of early acute acidosis.

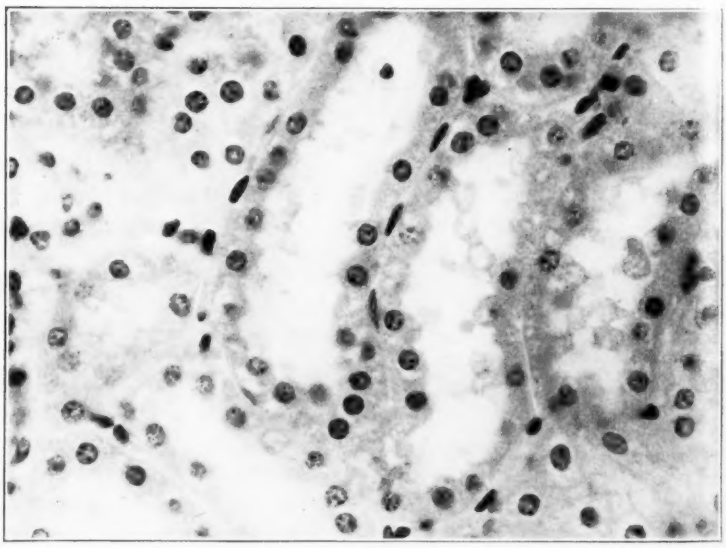

Fig. 2.—Convoluted tubules from the kidney of rabbit 7. The animal had received 18.6 Gm. of ammonium chloride over a period of seventeen days. The plasma carbon dioxide capacity was less than 20 per cent by volume two days before death, but due to the ingestion of sodium bicarbonate the plasma carbon dioxide had returned to 61 per cent by volume before death. The tubules are relatively normal except for the increased chromatin in the nuclei.

tuft and the capsule. In view of the negative observations in the glomeruli of the other animals, this must be attributed to the superimposed infection.

The left kidney was removed from rabbit 14 one month after the animal's plasma carbon dioxide had fallen to 10.7 per cent by volume. At this time the urine contained all types of casts in great numbers and a three plus albumin reaction. The blood urea nitrogen was 28 mg. per hundred cubic centimeters of blood. By way of treatment the animal was given sodium chloride, 4 Gm. daily by stomach tube, for two days. At the time of operation, one month later, the results of all tests were normal, except that there was a trace of albumin in the urine. Macroscopically and microscopically, the kidney removed for biopsy was normal with the exception of a few casts in some of the collecting tubules.

TABLE 2.—*Mild Acidosis*

	Duration of Experimental Period	Dosage of Drugs Administered	Urine Observations: Average p_H	Urine Observations: Average Albumin	Urine Observations: Casts	Carbon Dioxide per Cent by Volume: Average	Carbon Dioxide per Cent by Volume: Lowest	Hours Postmortem Cause of Death	Microscopic Kidney Observations
[illegible]	24 days	650 cc. N/10 HCl	5.6	+	Occasional hyaline and granular	59	59	? <17 Pneumonia	Postmortem swelling of tubular epithelium; serous precipitate in capsular space; spontaneous nephritis
[illegible]	2 mo.	1,850 cc. N/10 HCl 6 Gm. NH_4Cl	6.0	++	Occasional hyaline and granular	61	58	<3	A few pyknotic nuclei in tubular epithelium; spontaneous nephritis
16	2½ mo.	3,125 cc. N/10 HCl	6.0	Trace	Hyaline, terminally all types	56	34	0 Killed	Serous and cell débris in tubule; many pyknotic nuclei; slight spontaneous nephritis
15*	13 days	13 Gm. $CaCl_2$	...	+	0	57	55	.....	Same as 16; also convoluted tubular epithelium swollen; no spontaneous nephritis
	7 mo.	5,570 cc. N/10 HCl, 42 Gm. NH_4Cl	5.5	++	All types in moderate numbers	56	30	<5	

* There was an interval of six weeks between the two experimental periods.

During the following seven and a half weeks the animal received 22 Gm. of the ammonium chloride. In the middle of this period a severe acidosis developed. The plasma carbon dioxide capacity was reduced to 13.7 per cent by volume. The animal recovered from this, however, and at the time it was killed, the plasma carbon dioxide capacity was 25 per cent by volume; the urine showed a plus one albumin reaction and a few of all types of casts. Grossly, the kidney was somewhat pale but otherwise normal and weighed just under 9 Gm. Microscopically, the changes already described were found but to a less marked degree. Only occasional pyknotic epithelial nuclei were found, and the cytoplasm was less granular, swollen and vacuolated. There were a few scars of spontaneous nephritis.

Rabbit 6 was operated on and his right kidney removed at a time when his plasma carbon dioxide capacity was 41 per cent by volume. The urine had a p_H of 5.1 albumin $+++$, and showed hyaline and granular casts. There was severe bleeding at the time of the operation; the animal failed to gain weight afterward. He was finally killed three weeks later because of a stitch abscess which persisted and extended in spite of treatment. The abscess had involved the peritoneal wall at the site of the incision, and the intestines in the vicinity were matted together by dense adhesions. In spite of this secondary infection, the condition

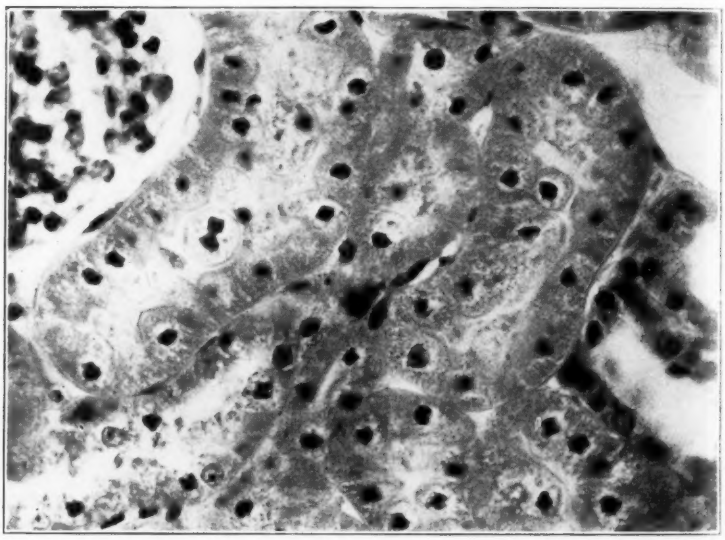

Fig. 3.—Convoluted tubules from the kidney of rabbit 6, removed at operation one year after the onset of acidosis. The plasma contained 41 per cent by volume of carbon dioxide. The marked pyknosis of the nuclei, with swelling and granulation of the cytoplasm is characteristic of protracted acidosis.

of the remaining left kidney, fig. 3, was somewhat better than of that removed at biopsy. The epithelium was not so swollen, and the pyknosis of the nuclei had in part disappeared. The kidney removed at biopsy showed the changes already described.

Of the four animals, table 2, that at no time contracted a severe acidosis, three died unexpectedly and autopsy was not performed immediately. Rabbit 16, which was killed, therefore furnishes the best example of this group. The same changes in convoluted tubules but to a less marked extent, were found microscopically.

The six control animals lived in the laboratory for from one month to sixteen months. All but one were killed and autopsy immediately performed. The animals that were kept ten months and longer occasionally showed a trace of albumin and, in some instances, a plus albumin reaction in the urine. This was most often associated with the spontaneous development of an acid urine. Three of the animals had hyaline and finely granular casts at times. The albumin and casts persisted in the case of no. 9 who at autopsy showed extremely extensive spontaneous nephritis. All had at least a few pits in the surface of their kidneys which microscopically were due to localized areas where tubules were collapsed, accompanied by round cell infiltration and connective tissue proliferation.

GENERAL BODILY REACTION OF RABBITS

The weight curve went down whenever the animals acquired a severe acidosis or a moderate acidosis extending over a long period of time. At autopsy the body fat was much decreased.

Pathologic changes elsewhere than in the kidneys were conspicuously absent. The aorta was examined particularly with reference to the development of arterial lesions, but only the small plaques which represent spontaneous degeneration of the media were found.

Rabbit 6 had progressive softening of his teeth during the last two months of his life, so that when he died the lower front teeth were practically gone. Dr. P. R. Howe had two of the teeth analyzed for calcium and found them deficient. The bones of the skull were so thin that they could readily be cut with an ordinary scissors. After twenty-four hours in Zenker's solution, they could be sectioned with a microtome. The long bones did not show any gross thinning, but the ribs were extremely soft. Loss of calcium and of fat in experimental acidosis has already been reported by Goto.[17] The epithelium of the lungs of this animal, no. 6, was vacuolated as though undergoing hydropic degeneration.

When an animal has severe acidosis, his respirations become slow and deep. His head is retracted. He sits quietly unless disturbed, and when he attempts to walk, he falls toward one side. Later, he lies on one side and exhibits spasmodic twitching of the extremities.

CHRONIC ACIDOSIS IN DOGS

Seven female mongrel dogs were used for the experiment. They ran together on the roof of the building during the day and occupied separate pens at night. Their diet consisted of Spratt's Dog Biscuit and meat. They all had the mange and were treated with sulphur ointment. It persisted in only one, no. 3.

17. Goto, Kingo: Mineral Metabolism in Experimental Acidosis, J. Biol. Chem. **36**:355 (Nov.) 1918.

Experimentally the dogs were treated in the same manner as the rabbits, except that the plasma carbon dioxide determinations were made much less frequently because the onset of acidosis in the dogs was more gradual.

EXPERIMENTAL RESULTS

In table 3 are summarized the experimental procedures in the five animals who were given ammonium chloride, calcium chloride and tenth normal hydrochloric acid. About two weeks after the onset of treatment, the specimens of urine showed a faint trace of albumin. It was

TABLE 3.—*Acidosis in Dogs*

Dog	Wt., Kg.	Duration of Experimental Period	Dosage of Drugs Administered	Urine Observations: Average p_H	Urine Observations: Average Albumin	Urine Observations: Casts	Carbon Dioxide per Cent by Volume: Average	Carbon Dioxide per Cent by Volume: Lowest	Hours Post-mortem Cause of Death	Microscopic Kidney Observations
1	14	4 mo.	56 Gm. NH_4Cl, 498 Gm. $CaCl_2$	6.0 Terminally 4.9	+	Hyaline, granular, in moderate numbers	30	21	0 Killed	Convoluted tubular epithelium vacuolated; nuclei showed karyolysis and occasional pyknosis; casts in collecting tubules; spontaneous nephritis
2	17	5½ mo.	26,590 cc. N/10 HCl, 124 Gm. NH_4Cl, 519 Gm. $CaCl_2$	5.9	Trace	Hyaline casts in about one half the examinations	45	31	..	Animal showed leukocytes and bacteria in the urine and the experiment was stopped
3	15	5 mo.	35,475 cc. N/10 HCl, 196.5 Gm. NH_4Cl, 171.5 Gm. $CaCl_2$	5.9	Trace	A few hyaline	40	27	..	Urine free from albumin and casts six weeks after stopping acid
4	17	3½ mo.	27,865 cc. N/10 HCl, 202.5 Gm. NH_4Cl, 227.0 Gm. $CaCl_2$	6.0	Trace	Occasional hyaline and granular rare cellular	42	32	..	Urine clear of casts in two weeks, of albumin in four weeks after treatment
5	12	5 weeks	207 Gm. $CaCl_2$	5.9	Trace	Occasional hyaline	..	..	..	Urine returned to normal in two weeks

not until acidosis was well established, about 35 per cent by volume carbon dioxide, that casts appeared constantly and then only in small numbers. With the exception of dog 1, which was pressed to a point where it became necessary to kill her, the albumin test was never more than plus one. The urine p_H did not vary between wider limits than 5.7 to 6.1 during the whole course of the experiment. Two dogs were starved for seven days but still maintained the same urine p_H even when given 4 Gm. calcium chloride by stomach tube.

Terminally, when dog 1 had a plasma carbon dioxide capacity of 21 per cent by volume, her urine p_H fell to 4.9; she had a two plus albumin

reaction and all types of casts in considerable numbers. She was killed because she had lost weight and vomited every thing that she ate or drank.

The right kidney weighed 70 Gm., the left 75 Gm. This is above normal weight for a 14 Kg. dog.[18] The capsule stripped readily, although the surface of the kidney was irregularly pitted. It presented the same picture as that of the spontaneous nephritis kidney in a rabbit. On section abnormalities were not noted grossly, with the exception of the infrequent fine white striations radiating in from the capsule and caused by the spontaneous lesions. All the other organs were also normal in appearance.

Microscopically, the convoluted tubules of the kidney were slightly swollen and showed extensive vacuolization suggesting hydropic degeneration. The nuclei were irregular in shape, usually larger than normal and pale. There were casts in the collecting tubules. There was no intertubular cellular proliferation. The picture as before was similar to that of cloudy swelling.

In addition to this change, which may be attributed to the acidosis, there were localized areas of spontaneous nephritis. These consisted in proliferation of the epithelium of the capsule with hyalinization and obliteration of the capsular space. This usually involved two or three contiguous glomeruli. The adjacent tubules were collapsed. An occasional small arteriole showed hyaline change. Goodpasture[18] described similar changes. MacNider[19] also describes spontaneous lesions in the dog's kidney. One animal that was killed as a control had smaller lesions of a less marked character in the glomerular tufts resembling those described by MacNider.

Of the other four animals, experimentation was stopped on no. 2 because she developed an infection of the urinary tract. The calcium chloride was stopped on the other dogs when the results from no. 1 were found to resemble those obtained on rabbits. The specimens of urine became free from casts and albumin in from two to six weeks.

In summary, therefore, the effect of an acidosis on dogs' kidneys was similar to that on rabbits' kidneys. An acute degeneration of the epithelium of the convoluted tubules resembling cloudy swelling resulted, which did not produce any of the reaction normally associated with a chronic process. The main difference between the dogs and the rabbits was the extreme difficulty in forcing the dogs to form a more than normally acid urine.

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18. Goodpasture, E. W.: Anatomical Study of Senescence in Dogs with Especial Reference to the Relation of Cellular Changes of Age to Tumors, J. M. Research **38**:127 (May) 1918.

19. MacNider, W. deB.: A Pathological Study of the Naturally Acquired Chronic Nephropathy of the Dog, J. M. Research **34**:177 (May) 1916.

COMMENT

Rabbits have been used extensively for work in experimental nephritis. Often much encouragement has been derived from the appearance in the urine of large quantities of albumin and numerous casts. Both are readily obtained in rabbits if the animal is forced to excrete an acid urine for a few days. Even when the irritation is carried over as long a period of time as a year, and the acidosis is forced to a point of almost lethal severity, with a resulting three plus albumin reaction and all types of casts, the injury proves microscopically to be only an acute tubular one resembling cloudy swelling. No permanent or chronic injury to the kidney is effected, and repair may take place rapidly and completely when the acidosis is stopped.

In carniverous dogs the same transitory type of injury to the tubular epithelium accompanies an acidosis. The animal protects himself against the development of an acid urine efficiently, however, and the albumin and casts are slower to appear and small in quantity until a drop in the p_H of the urine occurs.

The experimental production of nephritis with uranium nitrate is accompanied by acidosis. The fact as reported by MacNider [20] and Goto [11] that the toxicity of uranium nitrate is diminished by sodium carbonate may well depend on the neutralization of acids which are causing destruction of tubular epithelium. The same condition probably accounts for the diminution of albumin and casts in certain human patients with nephritis following alkali therapy as reported by Hösslin [4] and others.

It is also interesting, in view of the use of calcium and ammonium chloride to relieve tetany and edema, that such large quantities may be given to animals over long periods of time, and that such a severe acidosis may be incurred apparently without any permanent injury.

Our results emphasize the importance that an acid urine may have in producing the clinical picture of an injured kidney. Post and Thomas [21] find that in a large majority of patients with orthostatic albuminuria, neutralization or alkalinization of the urine by administering alkaline salts or by regulating the diet prevents the development of the albumin and casts. We are at present trying to confirm this and to determine urine p_H in patients with orthostatic albuminuria.

Another circumstance under which albumin and casts occur in the urine of a person who does not have nephritis is following severe muscular exercise. At this time the urinary acidity is increased. Bornstein

20. MacNider, W. deB.: The Inhibition of the Toxicity of Uranium Nitrate by Sodium Carbonate, J. Exper. Med. **23**:171 (Feb.) 1916.

21. Post, W. E., and Thomas, W. A.: Orthostatic Albuminuria, J. A. M. A. **80**:293 (Feb. 3) 1923.

and Lippmann [22] report that giving sodium bicarbonate by mouth lessens or does away with the albumin and casts from this cause.

SUMMARY

Calcium chloride and ammonium chloride both increase the acid metabolism when injected into the stomach of an animal.

Rabbits were given varying doses of tenth normal hydrochloric acid and ammonium chloride over periods of time extending from eleven days to one year. The plasma carbon dioxide capacity was lowered, and the animals excreted an acid urine. Casts and albumin were obtained constantly throughout the experimental period. At autopsy, however, the only demonstrable pathologic change in the kidney was acute degeneration of the convoluted tubules, similar to cloudy swelling, but also accompanied by marked pyknosis of the nuclei in cases of longer duration. When acid-forming substance was stopped, the kidney promptly returned to normal.

The results with dogs were comparable except that a greater dose of chloride had to be given in order to produce an acidosis, and that there were less albumin and casts.

The possible causal relation of acidosis to orthostatic albuminuria following strenous exercise is discussed.

I wish to thank Miss Lewis of the Peter Bent Brigham Hospital for the Bun determinations on rabbit 14. This was the only rabbit who showed any retention of blood urea nitrogen.

22. Bornstein, A., and Lippmann, A.: Weitere Beiträge zur nicht Nephritischen Albuminurie, Ztschr. f. klin. Med. **86**:345, 1918.

HEMORRHAGIC FOCAL GASTRODUODENAL LESIONS

PRELIMINARY REPORT OF THREE CASES *

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At the present time a large number of histories are being reviewed of patients who came to the Mayo Clinic complaining of gastro-intestinal hemorrhage. In this study only benign gastroduodenal lesions are included. In most of the series of cases that came to operation ulcers, gastric, duodenal or gastrojejunal, were found. There was, however, a surprisingly large number of cases in which a definite ulceration was not demonstrable at the operating table. In some of these, there were gastric, duodenal or esophageal varices; in a few, there was evidence of marked hepatitis; in others, splenomegaly or cirrhosis of the liver, and in a certain number it was assumed that a blood dyscrasia was responsible for the hemorrhages. Again, in other instances, some pathologic conditions of the gallbladder or appendix were found, and it was assumed that the condition was probably one commonly termed "gallbladder bleeding" or "appendiceal bleeding."

In some of these patients, as well as in others in whom there was no obvious cause for the hemorrhage, some unusual condition was found about the pylorus or in the duodenum. The operating surgeon discovered a number of dense adhesions about the pylorus, an edematous condition of the duodenum, stippling of the duodenum, and other conditions. In most patients the roentgenologic examination failed to show a deformity in the stomach or duodenum, and the chemical investigation of the stomach did not show anything unusual. In some, the concentration of acids was high, but this was not a consistent observation. The history of dyspepsia, although not characteristically that of ulcer, in the presence of hemorrhage led, in the majority of these cases, to a diagnosis of peptic ulcer; in many of them laparotomy was advised. If the history had not included the complicating factor of bleeding, the probability is that the operation would not have been advised.

The possible relationship of focal gastroduodenal lesions to this condition was investigated because in many of these cases there was a history of acute infections, such as tonsillitis, adenitis, or acutely swollen joints just prior to the onset of bleeding. In this connection the obser-

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vations of Boas,[1] Husemann,[2] MacCarty,[3] Judd,[4] Roeder [5] and Konjetzny [6] became of interest.

Roeder investigated the question of duodenitis and inferred that it is a relatively frequent condition. According to his description of the acute condition, the organ is considerably reddened and generally surrounded by cobweb-like or plastic inflammatory, peritoneal adhesions. He believes that the chronic type is common, and describes characteristic cobweb-like peritoneal adhesions surrounding the first portion of the duodenum, attached at times to the liver and to the gallbladder. The walls of the duodenum feel thickened, and the peritoneal coat seems congested.

MacCarty, in discussing duodenitis, writes:

> There is cellular destruction, congestion, edema and migration of leucocytes. The condition is seen as localized and also diffuse lesions; when diffuse, the appearance of the organ at exploration is not readily confused with duodenal ulcer; but when it is localized, the external appearance of the serosa is indistinguishable from that seen in association with small ulcers.

Boas and, subsequently, Husemann and many German writers have described acute, shallow, submucous ulcers scattered over the surface of the stomach and duodenum. At times these are complicated by gross hemorrhage.

Judd describes a duodenitis type of ulcer. He distinguishes this from the usual type of ulcer by the absence of distinct and demonstrable crater formation. If the surface of the mucous membrane is examined closely, single or multiple pin-point ulcers may be found. Both the submocosa and the muscularis are usually infiltrated with round cells which may extend a little distance into the tissues of the wall of the duodenum. He mentions the occasional complication of hemorrhage. He believes, however, that the bleeding associated with this kind of duodenitis is slight.

Konjetzny considered the possible relationship between chronic gastritis and chronic ulcer. He studied large series of preparations of resected stomachs and subjected these to thorough anatomic analysis. He found evidence of diffuse or focal gastritis in practically all those cases in which gastric ulcer was demonstrated. He also found similar lesions in those cases in which a duodenal ulcer was demonstrated.

1. Boas, Ismar: Diagnostik und Therapie der Magenkrankheiten nach dem heutigen Stande der Wissenschaft bearbeitet, Leipzig, G. Thieme, 1890-1893.
2. Husemann, T.: Die Gastroenteritis-Epidemic von Christiania (November, 1888), Deutsche. med. Wchnschr. **15**:960, 1889.
3. MacCarty, W. C.: Excised Duodenal Ulcers: A Report of Four Hundred Twenty-Five Specimens, J. A. M. A., **83**:1894 (Dec. 13) 1924.
4. Judd, E. S.: Pathologic Conditions of the Duodenum, Journal-Lancet, **41**:215, 1921.
5. Roeder, C. A.: Duodenitis, Nebraska M. J. **9**:252, 1924.
6. Konjetzny, G. E.: Die chronische Gastritis des Ulcusmagens, Zentralbl. f. Chir. **50**:1026, 1923.

The following cases are submitted because they present some interesting and unusual lesions about the pylorus, about the stoma and in the duodenum. In all of these cases, hemorrhage rather than dyspepsia was the prominent symptom.

REPORT OF CASES

CASE 1.—A chemist, aged 34, came to the clinic complaining of hemorrhages from the stomach. For about twenty years he had had occasional spells of dyspepsia, characterized at times by heartburn and vomiting. With the exception of tonsillitis and pleurisy, there was no history of any previous disease of importance. His history was indefinite; but there was apparently some relief from his symptoms after the taking of soda. In 1915, he had had an acute attack of gastro-intestinal disturbance which was diagnosed as ptomaine poisoning. The stools were dark, and he vomited small amounts of a black gastric content, which he believed contained altered blood. Four years later, he again suffered from pain in the epigastrium with vomiting; there was occasional diarrhea, and the stools sometimes contained blood. For about a week following this attack he experienced slight epigastric pain. Six months later, he had a similar experience. He again vomited blood and noticed tarry stools. He felt slight pain in the back, and on two or three occasions he lost consciousness. At that time he did not complain of any definite epigastric distress. In 1921, six years after the onset of the symptoms, he began to lose weight, and he occasionally felt slight supraumbilical pain which usually reached its maximal intensity three or four hours after meals. At rare intervals he experienced rather acute transitory colicky pain in the epigastrium, which food and soda relieved temporarily. Between 1921 and 1925, he had had periodic spells similar to this. Two months before admission, several days after one of these attacks, during the course of which he felt extremely weak, he vomited blood and passed some tarry stools. Since that time, he had experienced almost constant, although slight, epigastric distress.

He was a slightly pale, thin man who had lost considerable weight. The heart and lungs were normal. The abdomen, with the exception of slight tenderness over the entire hypogastrium, did not reveal anything abnormal. The blood pressure was normal. The hemoglobin was 78 per cent, and the erythrocytes numbered 4,400,000. A complete differential count revealed nothing of significance. Platelets numbered 168,000. The calcium time, coagulation time and bleeding time were within normal limits. Careful investigation did not reveal any evidence of blood dyscrasia. Repeated roentgenologic study of the stomach and duodenum failed to show any evidence of a deformity. Roentgenograms of the chest and colon were also negative. Gastric acidity gave titration values of 70 for total acid and 54 for free hydrochloric acid; 150 cc. of contents was withdrawn. Because of the history of dyspepsia complicated by hemorrhage, an operation was advised. Exploration revealed a small hemorrhagic spot on the anterior surface of the duodenum. The surgeon, however, was not certain that there was an ulcer. He said that there was considerable stippling about the duodenum, and suggested that it looked like duodenitis. The appendix was chronically inflamed and was removed. The cap of the duodenum was excised, and gastroduodenostomy was performed.

Prior to the operation, roentgenograms of the teeth had not been taken because the patient wore upper and lower plates. Since no other foci could be demonstrated as potential etiologic factors, it was decided to make a roentgen-ray examination of the alveolar processes; a few root tips were found. These were removed aseptically, and cultures were made. Three animals were injected intravenously with these emulsions, and in all cases they manifested duodenitis within twenty-four hours. There was an interesting similarity between the general characteristics of these lesions and those demontrated in the duodenum at operation (fig. 1).

CASE 2.—A man, aged 25, gave a history of pneumonia earlier in life and of repeated attacks of tonsillitis. He began to have stomach trouble at about the age of 12. During the succeeding six years, he had had periodic attacks of distress in the epigastrium. The description of them was rather vague. However, he remembered having had heartburn, especially several hours after meals. Ever since he was 18, the dyspepsia had been more noticeable. He had experienced pain several hours after meals and had felt better after he had taken soda or a small amount of food. Occasionally he suffered severe pain in the epigastrium, and the pain passed through to his back. In 1921, when he was 21, his physician decided that the symptoms might be caused by appendicitis. Appendectomy was performed, but the symptoms continued as before. About eight months after the operation, he suddenly felt a severe pain in the epigastrium and went into a state of collapse. An emergency operation was performed, and a perforating ulcer was found. A purse-string was made about the ulcer, and gastro-enterostomy was performed. Shortly after this, he experienced

Fig. 1.—Specimen showing submucous hemorrhages in duodenum of animal twenty-four hours after intravenous injection of cultures obtained from extracted dental root in case 1.

symptoms similar to those manifested prior to the operation. The pain now began in the epigastrium and radiated downward. It had the same relationship to meals as the former distress. On one occasion before coming to the clinic he vomited some blood, and for several days following this the stools were tarry. After this episode, he was weak for some time.

He was a tall, thin, undernourished, nervous young man with a systolic blood pressure of 86 and a diastolic blood pressure of 50. The tonsils had been excised elsewhere. There was some evidence of infection about the root of one tooth. Titration of gastric acids showed values of 76 for total acids and 36 for free hydrochloric acid. There was no evidence of recent bleeding or retention. The roentgenologic examination revealed a deformed duodenum and a free and apparently normal gastro-enteric anastomosis. Because of the similarity of the symptoms to those before gastro-enterostomy, because of the lower reference of the pain and because of the high acidity and a history of bleeding, a diagnosis of secondary peptic ulcer, probably gastrojejunal, was made, and an operation was

advised. The stomach was adherent to the liver and was freed. There was a suggestive scar on the anterior wall of the duodenum, which was not definitely an ulcer. The gastro-enteric anastomosis was then disconnected and turned from left to right. The ring of the stoma when excised showed a number of highly injected areas which the operating surgeon believed were responsible for the hemorrhages. Convalescence was uneventful. Several weeks after the operation, the tooth which had been infected periapically was extracted aseptically. Cultures prepared from this were injected into animals. Indurated areas with stippling and submucous hemorrhages in the duodenum were promptly produced in the animals on which the experiment was performed. These lesions were similar to the injected areas found about the stoma in the patient. My co-workers and I felt justified in assuming that the hemorrhages in this case were caused by gastrojejunitis.

CASE 3.—A man, aged 58, came to the clinic complaining of gastric hemorrhages. There had been no other illness, with the exception of pleurisy and

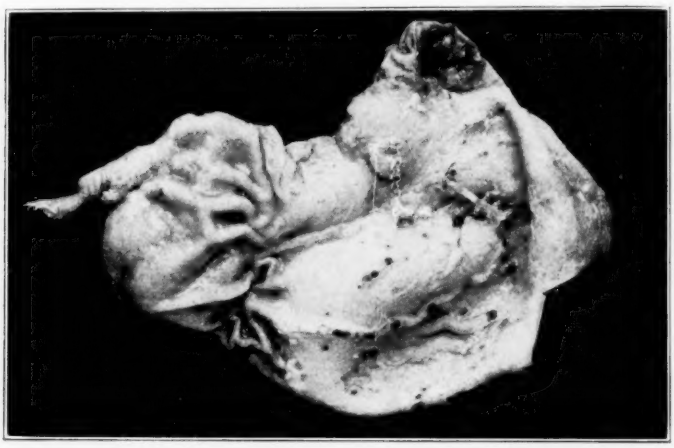

Fig. 2.—Specimen showing rabbit's stomach with multiple small hemorrhagic ulcers following the intravenous injection of cultures from an extracted tooth in a patient with hemorrhagic duodenitis.

several attacks of tonsillitis. For the last twenty-seven years he had had periodic spells of stomach trouble, with a gnawing sensation in the right upper abdominal quadrant. This distress would reach its maximal intensity several hours after meals. During the first of these attacks, he had vomited some blood and also had noticed tarry stools. These periodic spells of distress continued with only slight severity until 1906, eight years after the onset of symptoms, when he suffered a second hemorrhage. A third hemorrhage occurred six years after the second. After this complication, he felt well for fifteen years. Four weeks before his arrival at the clinic, there was another hemorrhage, which was followed in a week by further hematemesis. After the last attack he had occasional twinges of pain in the upper right abdominal quadrant, which were associated with slight flatulence and backache.

He was a pale, elderly man, but appeared to be well nourished. He had lost 16 pounds (7.3 Kg.) during the last month. The tonsils and teeth were infected. Abdominal palpation failed to reveal any masses. There was slight tenderness in the upper right abdominal quadrant. Careful investigation for possible blood dyscrasia was negative. Titration of gastric acidity showed total acidity 40 and

free hydrochloric acid 18; 125 cc. of gastric content was obtained. The first roentgenogram of the stomach was negative. The second showed a duodenal deformity which was assumed to be caused by ulcer. An operation was advised. The stomach and duodenum were normal. The gallbladder was slightly larger than normal, and there were some adhesions between it and the duodenum. The appendix contained a number of fecal stones and was chronically infected. The surgeon assumed that the appendix may have been the cause of the symptoms, including the hemorrhages, and he removed it. Convalescence was normal. Two teeth with periapical abscesses were extracted. Cultures were made and injected into animals. The resultant lesion in the rabbit involved the pyloric

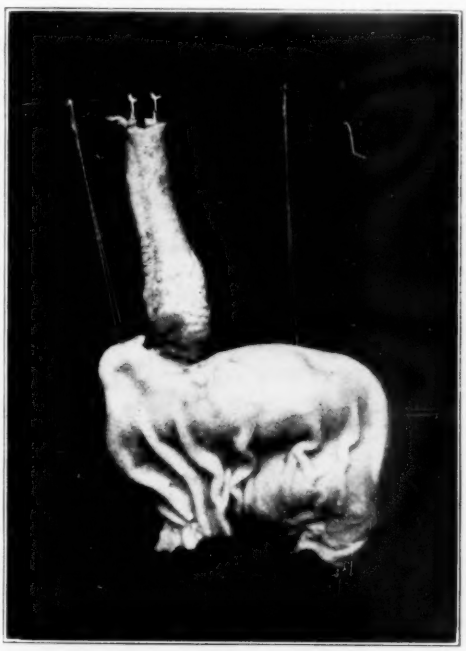

Fig. 3.—Section of stomach and duodenum of rabbit showing extensive submucosal hemorrhages. These followed injection of culture obtained from the extracted teeth in a patient with hemorrhagic duodenal ulcer.

end of the stomach. A large submucous blood clot was found in the region of the pylorus and small hemorrhagic areas in the duodenum. This led to the assumption that the hemorrhages were probably caused by infectious gastritis and duodenitis, which at the time of the operation had disappeared and had left only multiple adhesions about the duodenum (figs. 2 and 3).

COMMENT

These histories and case reports are typical illustrations of one group of patients in whom infectious lesions are probably responsible for gastro-enteric hemorrhages. They are additionally interesting and important because they stimulate speculation as possible forerunners of

chronic ulcer. This condition occurs frequently. Experimental work is being done to determine the specificity of certain strains of streptococci in the production of these lesions. Recently a number of these patients came under my observation. When an operation was performed shortly after the occurrence of hemorrhage, acute lesions were demonstrable in the potential areas of peptic ulcer; when the operation was postponed, and later advised mainly because of the history of hemorrhage, little was found to account for the bleeding. In these patients all possible sources of focal infection have recently been removed, and a bland diet of high caloric content has been advised. Thus far the results of these measures have been extremely encouraging. It is, of course, too early to attempt to draw definite conclusions from the data which are obtainable at the present time. It is my opinion, however, that many of these cases of so-called "appendiceal bleeding" or "gallbladder bleeding" are probably caused by acute lesions in the stomach or about or in the duodenum. These lesions are known to heal promptly by the institution of the usual methods of treatment which promote healing and by the removal of all deterrent factors.

HODGKIN'S DISEASE

WITH PREDOMINANT LOCALIZATION IN THE NERVOUS SYSTEM; EARLY DIAGNOSIS AND RADIOTHERAPY *

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Nearly a century ago, Hodgkin [1] first described the disease that now bears his name. In his original series of cases—of which five at most were authentic—there was involvement of: (*a*) the lymph nodes in all cases; (*b*) the spleen in four cases; (*c*) the tonsils and the lymphoid tissues of the base of the tongue and pharynx in one case, and (*d*) the testicle possibly in one case.

In 1859 Wilks [2] reported one case of Hodgkin's disease in which he noted, in addition, invasion of the liver and kidneys. Six years later,[3] he published further observations showing the specific lesions also in the lungs.

In 1865, Cornil and Ranvier,[4] from a study of the literature and their own cases, had noted that Hodgkin's disease was more than a mere "affection of the absorbent glands and spleen." In addition to involvement of the lymph nodes and spleen, they found the specific lesions in the following organs and tissues: the skin, intermuscular tissues, subcutaneous tissues, bones, thymus, lungs, stomach and intestines.

Simultaneously with the publication of these articles in England and France, similar studies appeared in Germany, chief among which were those of Billroth,[5] Wunderlich,[6] Virchow [7] and Cohnheim.[8] It was the great merit of Cohnheim to perceive the generalized nature of Hodgkin's disease and its close similarity to leukemia in its widespread systemic dissemination. The new winged word, pseudoleukemia, coined by

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2. Wilks, S.: Enlargement of Lymphatic Glands with Deposit in Spleen and Other Organs, Tr. Path. Soc., London **11**:257, 1859-1860.
3. Wilks, S.: Cases of Enlargement of the Lymphatic Glands and Spleen (or Hodgkin's Disease), Guy's Hosp. Rep. **11**:56, 1865.
4. Cornil, A. V., and Ranvier, L. A.: Man. d'Histologie Pathologique, Paris 1869, p. 251.
5. Billroth, C.: Beitr. z. path. Histologie, 1858, pp. 168-171.
6. Wunderlich, C. A.: Zwei Fälle von Progressiven Multiplen Lymphdrusen Hypertrophien, Arch. f. Phys. Heilk. **2**:123, 1858; Pseudoleukamie, Arch. d. Heilk., Leipzig **7**:531, 1866.
7. Virchow, R.: Die Krankhaften Geschwülste, 1864-1865, vol. 2, pp. 728-739.
8. Cohnheim, J.: Ein Fall von Pseudoleukamie, Virchow's Arch. **33**:451, 1865.

Cohnheim, may have been inappropriate and confusing to characterize the microscopic changes of Hodgkin's disease, as stated by Virchow and others.[9] The immediate popularity, however, of pseudoleukemia as a clinical concept and synonym for Hodgkin's disease and its almost universal adoption by the medical world for a great many years attests the historically and philosophically significant fact that Cohnheim's generalization of the systemic nature of Hodgkin's disease, based on the study of a single case, had struck a responsive cord in the minds of all students of this disease.

With medical attention now fully interested in this malignant malady of obscure etiology, numerous case reports began to appear in the literature in which ever wider areas of invasion were recorded until the protean and systemic aspects of Hodgkin's disease were fully established. And thus, in 1879, Gowers,[10] in his comprehensive contribution on Hodgkin's disease, gave details concerning the lesions not only in the lymph nodes and spleen, but also in the skin, intermuscular tissues, bones, brain, soft palate, pharynx, tonsils, esophagus, stomach, small intestine, large intestine, liver, pancreas, peritoneum, thyroid, thymus, trachea, lungs, pleura, diaphragm, pericardium, heart muscle, suprarenals, kidneys, testes and ovaries.

The protean aspects of Hodgkin's disease thus stressed by Gowers received further corroboration and addition by a host of investigators, among whom were Birch-Hirschfeld,[11] Osler,[12] Ehrlich,[13] Murray,[14] Longcope,[15] Ziegler,[16] Ewing,[17] Symmers,[18] Sternberg[19] and others. As a result of their investigations, it was repeatedly and conclusively proved that not a single organ or tissue had escaped invasion in Hodgkin's disease.

Simultaneously with the recognition of the widely disseminated and protean character of Hodgkin's disease, repeated and numerous obser-

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9. Hutchinson, R.: Hodgkin's Disease, Lancet **1**:1404, 1904.
10. Gowers, W. R., in Reynold: System of Medicine, Philadelphia, 1879, vol. 5, p. 306.
11. Birch-Hirschfeld, in von Ziemssen: Cyclopedia of the Practice of Medicine, 1877, vol. 16, p. 829.
12. Osler, W., in Pepper: System of Medicine, Philadelphia, 1885, vol. 3, p. 921.
13. Ehrlich, P., in Nothnagal: Specielle Pathologie and Therapie, 1898, vol. 8, p. 81.
14. Murray, G. R., in Allbutt and Rolleston: System of Medicine, 1908, vol. 4, p. 459.
15. Longcope, W. T.: Oxford Medicine, 1921, vol. 4, p. 1.
16. Ziegler, K.: Die Hodgkinische Krankheit, Jena, 1911.
17. Ewing, J.: Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1922.
18. Symmers, D.: The Clinical Significance of the Pathological Changes in Hodgkin's Disease, Am. J. M. Sc. **167**:157 (Feb.) 1924; **167**:313 (March) 1924.
19. Sternberg, C.: Lymphogranulomatosis, Klin. Wchnschr. **4**:529 (March) 1925.

vations had revealed its marked variation not only in the duration, character and acuteness of its clinical course, but also in its elective localization in different regions, tissues and organs in different persons. Although it is unquestionably true that in large series of cases the superficial lymph nodes are the first to attract clinical attention, numerous case reports have appeared in the literature in which the primary and predominant clinical localization occurred in the skin,[20] bones,[21] lachrymal and salivary glands,[22] nose,[23] tonsils,[24] trachea and bronchi,[25] esophagus,[26] stomach,[27] intestines,[28] liver,[18] spleen,[18] pancreas,[29]

20. Saalfeld, C.: Zur Frage der Hautlokalization der Lymphogranulomatose, Arch. f. Dermat. u. Syph. **148**:158, 1924. Shelmire, B.: Hodgkin's Disease of the Skin, South M. J. **18**:511 (July) 1925. Reinsberg, V., and Kadlicky, R.: Lymphogranulomatosis cutis et conjunctivae bullei, Acta. derm.-venereol. **5**: 377 (Oct.) 1924.

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22. Mickulicz, J.: Ueber eine eigenartige symmetrische Erkrankung der Thranen und Mundspeichel drusen, Beitr. z. Chir. Festschr. gewidmet T. Billroth, 1892, pp. 610-630. Haeckel, H.: Beitrag zur Erkentniss der Symmetrischen Erkrankung der Thranen und Mundspeicheldrusen, Arch. f. klin. Chir. **69**:191, 1903.

23. Harris, T. J.: Hodgkin's Disease of the Nose, Laryngoscope **35**:34 (Jan.) 1925.

24. Hodgkin (footnote 1). Sternberg (footnote 8).

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abdominal lymph nodes,[30] thymus,[31] mediastinum,[32] heart,[33] hemopoietic system [34] and nervous system.[35]

The invasion of the nervous system in Hodgkin's disease first reported by Murchison [30] has since been noted by many observers, among whom were: Goodhart,[36] Gowers,[10] Osler,[12] Welch,[37] Ziegler,[16] Longcope,[15] Askanazy,[38] Dietrich,[39] Schmorl,[40] Sternberg,[19] Hecker and Fischer,[41] Weber,[42] Holmes,[43] Pancoast,[44] Saalfeld [45] and others.

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36. Goodhart, J. F. (footnote 35).

37. Welch, W. H. (footnote 35).

38. Askanazy, M. (footnote 21).

39. Dietrich (footnote 21).

40. Schmorl (footnote 21).

41. Hecker and Fischer (footnote 35).

42. Weber (footnote 35).

43. Holmes (footnote 21).

44. Pancoast (footnote 35).

45. Saalfeld, C. (footnote 19).

It is true that in the majority of instances the invasion of the nervous system was overshadowed by the extensive pathologic changes in the lymph nodes and viscera. That occasionally, however, the clinical course may be dominated almost entirely by the attack on the nervous system, is attested by the cases of Goodhart,[36] Askanazy,[35] Hecker and Fischer [41] and Walthard.[46]

However, in spite of the foregoing reports, the impression is still widely prevalent among physicians that the nervous system is so rarely involved in Hodgkin's disease as to be ignored in the differential diagnosis of diseases of the nervous system. Not only did I fail to see Hodgkin's disease mentioned in the standard textbooks on diseases of the nervous system, but even in the excellent recent monograph of Elsberg [47] on "Tumors of the Spinal Cord," the condition is ignored completely.

It, therefore, will be of considerable interest to report a series of ten of thirty-six patients with Hodgkin's disease observed at Montefiore Hospital during the years from 1914 to 1925, in which definite invasion of the nervous system was a striking clinical phenomenon. Some of these cases, which were of unusual clinical interest, will be reported in detail, while those of lesser value will be but briefly described.

REPORT OF CASES

Case 1.—*History.*—N. S., a man, aged 47, was admitted to the neurological service of Montefiore Hospital, Aug. 16, 1923, with a diagnosis of possible cord tumor. In May, 1921, the patient suddenly developed intense itching over the dorsal surface of his left forearm. There was not any visible eruption over the site of irritation. A few weeks later, a similar condition developed over the left upper outer thigh and scrotum. The itching was most intense at night, interfering with sleep. For two years the pruriginous condition continued unabated and was relieved only occasionally by local medication. In the meanwhile other symptoms appeared. In May, 1922, one year after the onset of the pruritus, the patient commenced to develop asthenia, fatigability and dyspnea on slight exertion. These symptoms grew slowly but progressively worse until May, 1923, when he was suddenly seized with severe cramplike, nonradiating pain in the upper part of the abdomen. He immediately consulted a physician, who diagnosed his condition as gastric ulcer. A roentgenologic study of the entire gastro-intestinal tract failed, however, to reveal any lesion. The abdominal pain kept recurring, and two or three weeks after onset, it began to radiate posteriorly to the dorsal spine. The colicky character gradually changed to a sharp, cutting and stabbing pain which radiated from the lower dorsal spine peripherally to the abdomen and down both lower extremities to the toes.

In June, 1923, the patient was admitted to a prominent hospital in New York where, after several weeks of observation and a most exhaustive study, including roentgen-ray examination and serologic tests, a diagnosis of spondylitis was made. The patient's condition gradually grew worse. In July, 1923, he began to develop symptoms of paraplegia and became bedridden. On Aug. 8, 1923, he was admitted to the neurologic service of Montefiore Hospital.

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46. Walthard, K. M. (footnote 35).

47. Elsberg, C.: Tumors of the Spinal Cord, New York, Paul B. Hoeber, 1924.

Examination.—The patient was moderately pale but well nourished in the trunk and upper extremities. His chest, lungs and heart were normal. On abdominal palpation, he revealed an enlargement of the spleen to 1 inch below the costal margin and a moderate enlargement of the liver.

Neurologically, he revealed an almost complete motor paralysis and a loss of sensation in both lower extremities with sphincteric involvement. There was atrophy of the muscles of the thighs and legs. Hyperesthesia and hypalgesia were present from below up to the sixth and seventh dorsal segments.

Roentgen-ray studies of the skull, spine, chest and gastro-intestinal tract failed to elicit any gross lesions. The blood and spinal Wassermann tests were negative. The spinal fluid showed a slight increase in pressure but did not present other abnormalities. A study of the blood chemistry and a colloidal gold test failed to reveal any abnormality. A blood count showed: red blood cells, 3,600,000; hemoglobin, 75 per cent; white blood cells, 11,600; polymorphonuclears, 55 per cent; small lymphocytes, 15 per cent; large lymphocytes, 28 per cent; eosinophils, 0.5 per cent; myelocytes, 1.5 per cent.

Treatment and Course.—After four weeks of observation, study and consultation with the heads of several departments, the consensus of opinion, with one exception, was in favor of a spinal cord neoplasm and operative intervention.

On Sept. 19, 1923, a laminectomy revealed an extradural tumor, 8 cm. in length, lying between the third and the seventh dorsal vertebrae. Its upper and lower poles were defined sharply. Its surface was smooth and glistening. The laminae overlying the tumor were intact with the exception of those of the sixth dorsal, which were eroded. The lateral limits of the tumor were ill defined, the neoplasm apparently extending circumferentially all around the cord. The thickened portion of the tumor measured about 2 cm. The dura and cord were compressed but not invaded by the neoplasm. However, only an incomplete removal of the tumor was possible which on pathologic examination was reported as a sarco-endothelioma (fig. 1).

The patient made an uneventful recovery, and a few days after the operation was able to move his lower extremities actively in bed. The sphincteric involvement, however, continued and radiotherapy was decided on.

On Jan. 20, 1924, the patient received his first radium application in the form of a pack over the dorsal spine at the site of the operation. This was repeated about once a week, in fractionated doses until Aug. 23, 1924. There was moderate improvement in the paraplegic symptoms until July, 1924, when he began to have remittent fever up to 102 F. He also developed generalized enlargement of the lymph nodes and spleen.

A biopsy of the enlarged inguinal lymph nodes showed pathologic changes similar to those of the extradural neoplasm (fig. 2). Both specimens were submitted to Dr. James Ewing, whose diagnosis was Hodgkin's disease.

The patient grew progressively worse, and died with symptoms of generalization and severe secondary anemia. Autopsy was not permitted.

Comment.—Among the the many features of clinical interest presented by this case, the diagnostic are the most instructive. For one year persistent pruritus was the only symptom present before the advent of constitutional symptoms—asthenia, fatigability and dyspnea on exertion. At the end of two years after onset, the initial symptoms or paraplegia appeared, simulating the symptoms in a gastric ulcer. The paraplegia was believed to be caused by a tumor of the cord; this belief was verified on the operating table. There was not any suggestion of Hodgkin's disease even after the pathologist's first diagnosis of sarco-endothelioma. Only when generalized lymphadenopathy devel-

oped was Hodgkin's disease suspected, and biopsy showed that this condition was present.

Why did this delay in diagnosis occur in a case which presented the highly suggestive clinical symptomatology of Hodgkin's disease with paraplegia, which has been described in the literature by Goodhart,[36] Osler,[12] Longcope,[15] Parkes-Weber,[42] Sternberg,[19] Askanazy[38] and others?

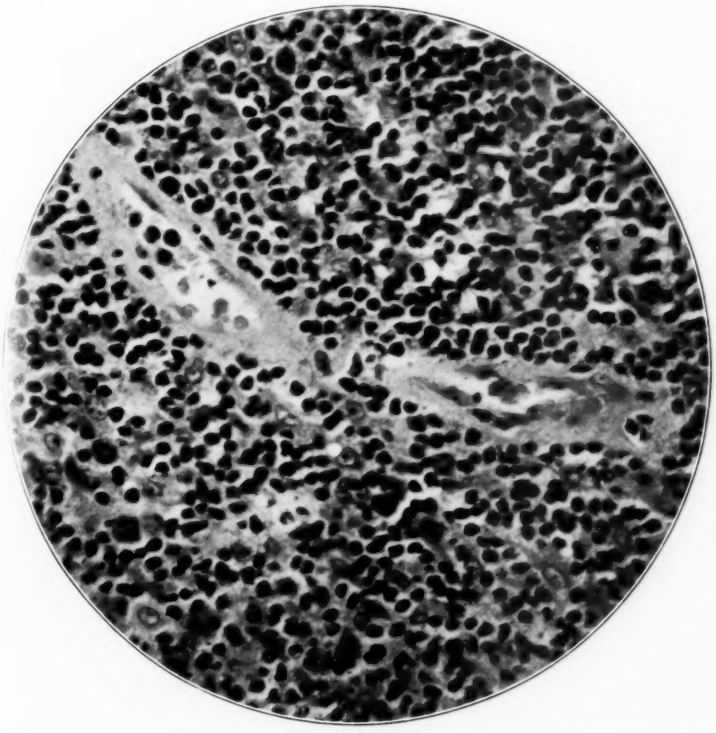

Fig. 1 (case 1).—Spinal cord neoplasm showing hyperplastic cellular stage of Hodgkin's disease.

The answer to this question involves the consideration and solution of two most important problems: one local and the other general.

The local problem involves the widely prevalent, erroneous, antiquated view that Hodgkin's disease is pathologically as well as clinically "an affection of the absorbent glands and spleen," with occasional deposits in other viscera. The abundant evidence previously detailed of the protean aspects and primary or predominant clinical localization

of Hodgkin's disease in practically every organ or tissue in the body, is still ignored in our textbooks and systems of medicine. It was, therefore, the absence of the stereotyped clinical picture of demonstrable primary enlargement of the lymph nodes which warded off the suggestion of Hodgkin's disease in this case, even though the enlargement of the liver and spleen, the secondary anemia, fatigability and dyspnea on exertion and the pruritus pointed to Hodgkin's disease as a possible cause of the paraplegia.

Fig. 2 (case 1).—Inguinal lymph node showing hyperplastic cellular stage of Hodgkin's disease.

The general problem is one of the most important and fundamental in clinical and institutional medicine; namely, the proper taking of the clinical history by the intern staff of hospitals and medical clinics. In medical institutions, public as well as private, the taking of the clinical history is most frequently if not invariably relegated to the care of the junior or senior intern, whose clinical experience is still immature and incomplete, and whose familiarity with the rarer types of disease

is, to say the least, extremely limited. Furthermore, in the rush of the routine work and the manifold duties devolving on the intern, the patient is not always allowed sufficient time to give a full and detailed account of his symptoms; nor is the intern sufficiently equipped to make a complete investigation of the minor symptoms, which are usually slighted, but which may sometimes be the important ones to give the clue to the diagnosis in a difficult case.

In the case under discussion the initial history obtained by the intern was that of an acute condition with rapidly developing paraplegia. The pruritus of two years' duration and the progressive asthenia, fatigability and dyspnea on exertion antedating the paraplegia did not appear in the early records of the history of the case. Only when the biopsy suggested the pathology of Hodgkin's disease did careful questioning elicit spontaneously the highly suggestive diagnostic symptoms of Hodgkin's disease as detailed in the later published records. The important lesson derived from the study of this case is the need for thorough clinical historical investigation by the experienced members of the visiting and consulting staff of hospitals and clinics. A physical objective examination alone is not always sufficient to establish a correct diagnosis in a difficult case. Certain symptoms registered in the patient's consciousness may be as highly diagnostic or even more so than many objective signs demonstrable to our unaided or even to our aided senses by all the modern laboratory methods of diagnostic precision.

CASE 2.—*History.*—M. S., a woman, aged 32, was admitted to Montefiore Hospital on April 16, 1925. Three years before admission she began to suffer from migrating pruritus in various regions of her body. The pruritus was intense and marked at night, interfering with sleep. A visible eruption was not present except when it was induced by vigorous scratching. A month or two after onset, she commenced to make the rounds of private physicians and various well known dermatologic clinics. A local skin condition was diagnosed and medication prescribed accordingly. When the remedies failed to relieve, "nervousness" was blamed for the persistency of the pruriginous condition in the absence of any visibly demonstrable skin lesions.

After two years of persistent pruritus, other symptoms began to appear. In April, 1924, she noted slight and painless enlargement of her right cervical lymph nodes. Gradually, she began to develop asthenia and anorexia. In September, 1924, she was suddenly seized with severe pain in her lower cervical and upper dorsal spine, radiating girdle-like peripherally. For three days the pain was acute and recurring; it then lessened gradually. With subsidence of the pain, progressive weakness of both lower extremities developed. At first the right limb felt heavy and weak and later the left. She commenced to stumble, and her gait became dragging. Toward the middle of December, definite paraplegia set in with sphincteric involvement—incontinence of urine and obstinate constipation.

On Dec. 18, 1924, she was admitted to a well known New York institution where physical examination revealed spastic paraplegia with a sensory level at the fourth dorsal segment to touch, pain and temperature. Vibration was lost to the costal border. Position sense was retained even in the toes. There was definite tenderness of the spine in the fourth to the sixth dorsal segment.

Examination of the spinal fluid was negative except for a 3+ globulin reaction. A blood count showed a slight secondary anemia. Roentgen-ray examination of the chest revealed the right diaphragm considerably higher than the left and the superior and posterior mediastinum filled with a large massive shadow probably caused by a new growth which had pressed the heart downward and to the left.

A diagnosis of extradural spinal cord tumor was made, and surgical intervention was decided on. At operation an extensive extradural tumor was found. It reached from the second thoracic laminae to below the fifth. The lower limit was not determined. The gross appearance of the tumor was that of sarcoma. Removal was not attempted.

Following the operation, the patient received several roentgen-ray treatments over the spine without any resulting improvement. On April 16, 1925, she was transferred to Montefiore Hospital.

Physical Examination.—On admission, examination revealed a well nourished, slightly pale, young woman. Her skin was darkly pigmented but did not present any eruption. There was an enlarged lymph node, the size of a lima bean, in the right cervical region.

The chest showed dilatation of veins in the infraclavicular regions, in the right side more than in the left side. There was marked upper retromanubrial dulness, caused by a large mass in the upper mediastinum demonstrated by roentgen-ray examination. The heart did not present anything abnormal. Her pulses were equal; the blood pressure was, systolic, 110, diastolic, 70.

The abdomen was tense and rigid. The liver and spleen, on percussion, were apparently enlarged. Both lower extremities were spastic, flexed and held in abduction. Both large toes were held in extension, and on touch both extremities began to go into clonic tremor.

On April 27, 1925, cervical lymph nodes were removed for pathologic examination (fig. 3). Dr. Seecof's report was: "Lymph nodes show striking diffuse fibrosis with areas of hyaline scarring. Complete loss of architecture. No germinal follicles. There are foci in which there are densely packed lymphocytes, numerous endothelial cells and an occasional endothelial giant cell. No eosinophils. Diagnosis, Hodgkin's disease, or lymphosarcomatosis." The slide was submitted to Dr. James Ewing, whose diagnosis was Hodgkin's disease.

On May 9, 1925, the patient was examined by Dr. Abrahamson, who reported: "The signs point to a high dorsal transverse myelitis which, in view of the history, is most likely due to Hodgkin's disease."

Treatment and Course.—The same day high voltage roentgen-ray treatment of the spine and mediastinum was started and repeated until March 10, 1925; three erythema doses were given over each area. The result was slow, moderate recession of paraplegia symptoms toward the end of 1925. The patient had regained control of urination. She could flex and extend her knees and could help herself out of bed on an invalid's chair, but she still showed considerable spasticity of her lower extremities. She was unable to stand up or sit up in bed without supporting herself with her hands. Her rectal sphincteric control had not been regained. The mediastinal mass had receded but slightly.

At present the patient is in excellent physical condition, but mentally she is miserable because of her incontinence, and because she has to remain in bed or be wheeled in a chair.

Comment.—The chief points of interest in this case are both diagnostic and therapeutic. As in case 1, an imperfect history of an acutely developing neurologic condition led to a diagnosis of a primary spinal cord neoplasm. At operation the tumor was found to be irremovable. Roentgen-ray therapy thoroughly carried out resulted in only

slight relief of the paraplegia. This emphasizes the great importance of early diagnosis and early radiotherapy in Hodgkin's disease, especially when the nervous system is involved. Notwithstanding the fact that the lesions in Hodgkin's disease are among the most sensitive and responsive to radiotherapy, this is true only in the stage of hyperplasia and abundant cellularity. In the late stages of Hodgkin's disease when marked fibrotic changes are present, little if any effect can be expected

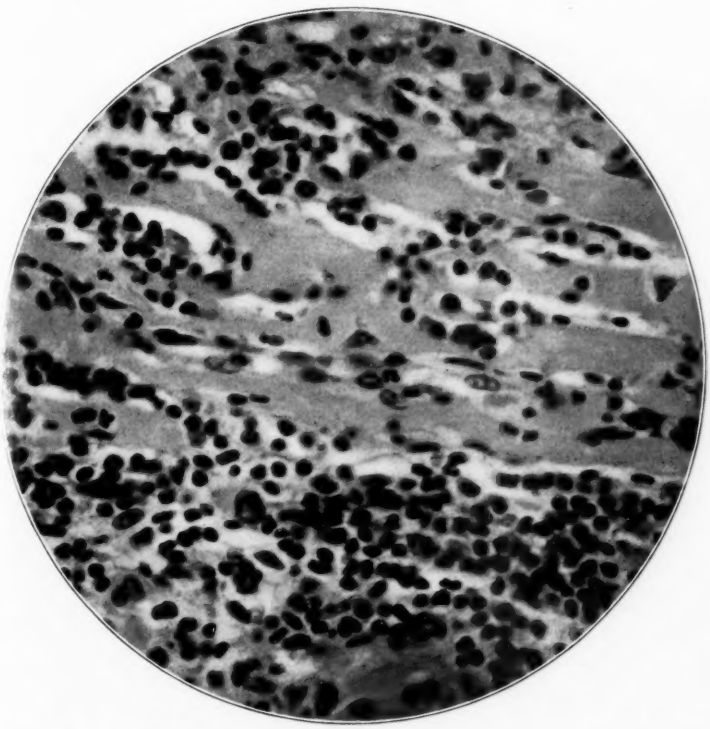

Fig. 3 (case 2).—Cervical lymph node showing commencing hyalinization in Hodgkin's disease.

from either radium or roentgen-ray treatments. This is true especially in lesions of the nervous system in which invasion or compression of the nervous elements for any length of time leads to irremediable degenerative changes which may persist even after the original damaging cause is removed.

CASE 3.—*History.*—A man, aged 29, a patrolman, was admitted to Montefiore Hospital, April 13, 1922, with a diagnosis of tuberculosis pleurisy with effusion and possibly Pott's disease of the spine. In February, 1921, while on night duty

during a heavy snow storm, the patient slipped and fell, striking the lower part of his spine. He was dazed but not unconscious. He lay for a few minutes with his left heel pinned under his spine, unable to rise until he was assisted by pedestrians. He continued on duty during the rest of that night and did not experience any difficulty in walking. The next day the calf of his left leg became swollen and painful. Although he was able to walk, the pain in his leg was considerable, and he stayed away from duty for the next three weeks. He then felt apparently well for several weeks until April, when he was suddenly awakened one night by severe sharp pain in the lower spine radiating laterally to both sides. The pain was most severe over the site of the former injury. For one month it kept recurring, worse at night, interfering with sleep. Toward the end of May, the pain disappeared completely. He felt perfectly well for the next three months until August, 1921, when the pain recurred in a most aggravated form. It was severe and constant day and night. Several physicians were consulted, but the diagnosis was doubtful, and the various remedies failed to relieve. Accordingly, he was admitted to a general hospital in New York City, where he remained under observation for six weeks. A complete study failed to furnish any clue to the underlying cause of his symptoms. Gradually the pain grew agonizing and began to radiate down both lower extremities. Repeated hypodermic injections of morphine had to be resorted to, with but temporary relief.

Discouraged because of the lack of improvement, the patient left the institution to return home. There his symptoms grew progressively worse. In October, 1921, he began to develop signs of spastic paraplegia with sphincteric involvement. In November, he was admitted to one of the largest hospitals in New York City where, after an exhaustive study, a definite diagnosis was not made. The consulting neurologist favored a diagnosis of Pott's disease of the spine, while the consulting orthopedist inclined to a neurologic diagnosis—probably spinal cord neoplasm.

Toward the end of December, 1921, there was a gradual spontaneous return of sensation in the thighs and partial regain of bladder control. In the early part of 1922, there was also partial return of power in both lower extremities.

In March, 1922, when he had recovered almost completely from his spastic paraplegia, he suddenly developed pain in the right side of his chest, accompanied by cough, fever and dyspnea. With the onset of his respiratory symptoms the long delayed diagnosis was finally pronounced as pulmonary tuberculosis with pleuritic effusion and Pott's disease of the spine, and he was transferred to the tuberculosis division of Montefiore Hospital, in the service of Dr. Maurice Fishberg.

Examination.—On admission, April 13, 1922, the patient was found well nourished and did not appear acutely ill. There was a pleural effusion filling one half of the right side of the chest. The heart was displaced to the left.

Neurologic examination by Dr. Abrahamson revealed a belt of hyperesthesia from the eighth to the twelfth dorsal segment on both sides, most marked from the eighth to the tenth. Below this hyperesthesia there was an area of normal sensation except in the fifth lumbar. The perianal area was normal. Cremaster reflexes were present, which were greater on the left side than on the right. There was constant extensor position of the left big toe. Points of exquisite tenderness to deep pressure and to percussion were present corresponding to the ninth dorsal spine and fourth lumbar. Edema was not present; no gibbus. Vibratory sense was diminished from the knees down on both sides and was lost in the perianal area. There was general motor weakness in the iliopsoas group and flexors of the thighs. There was a slight tendency to foot drop on the right side. There was an overflow incontinence of urine.

Tentative Conclusion.—This was a lesion of the bone or periosteum at the level of the eighth or ninth dorsal segment with a possibility of a secondary level at the fourth lumbar segment. Whether the lesion was tuberculous, as pleurisy

with effusion might indicate, or sarcomatous, could not be decided definitely without roentgen-ray examination.

The next day, April 18, roentgen-ray examination of the spine was negative for bone disease. The chest showed a dense homogeneous shadow occupying the entire right pulmonary field. The middle third of the shadow was slightly denser than the rest. The heart and mediastinal contents were displaced to the left.

On April 26, 1922, Dr. Maurice Fishberg expressed the opinion that, "The roentgen-ray observations are highly suggestive of a mediastinal tumor, the nature and origin of which are undetermined." The same day, for the first time in his life, the patient developed a severe epileptiform convulsion with marked frothing at the mouth and biting of his tongue. During the next few weeks he suffered from dull, frontal headaches radiating to the vortex.

For the first time enlargement of the right supraclavicular and of the left axillary lymph nodes was noted. A biopsy of one of these nodes resulted in a diagnosis of Hodgkin's disease.

Course of Illness.—The further course of this case, with the exception of one more spontaneous remission of a few months' duration was characterized by symptoms of generalization, marked mediastinal and pulmonary involvement, recurring severe pain in the spine and occasional severe epileptiform convulsions. Three days before his death, the patient developed a low muttering delirium, in which he died.

Comment.—The remarkable features of clinical interest in this case were: (1) the mode of onset with severe pain suggesting at first a traumatic spondylitis and later a transverse myelitis; (2) the repeated spontaneous remissions; (3) the development of mediastinal and pleuropulmonary involvement while the spastic paraplegia was apparently clearing up spontaneously, and (4) the repeated attacks of epileptiform convulsions which suggest invasion of the brain.

Until recently all the cases of Hodgkin's disease with epileptiform convulsions failed to show the specific pathologic process in the brain. Within the past few years, Hecker and Fischer,[41] Askanazy,[38] Saalfeld [45] and Holmes [43] reported the definite pathology of Hodgkin's disease in the brain and meninges.

CASE 4.—*History.*—Y. T., a woman, aged 40, was admitted to Montefiore Hospital on Aug. 14, 1920, and died Jan. 5, 1922.

In March, 1917, she experienced severe pain over the right shoulder. Two or three months later similar severe pain developed in the left thigh. Associated with the pain in the thighs were severe itching and asthenia. Anorexia and loss of weight followed gradually and became progressive.

Two and a half years after the onset of the pain in the right shoulder, evidence of mediastinal involvement and enlargement of the cervical lymph nodes was noted. In December, 1919, the patient was admitted to Mount Sinai Hospital, New York, where a biopsy of a lymph node showed Hodgkin's disease, and roentgen-ray examination revealed involvement of the spine and pelvic bones.

She died with symptoms of generalization on Jan. 5, 1922.

Autopsy.—This revealed numerous scratch marks on the skin and a large bulging mass on the anterior surface of the vertebral column in the region of the third, fourth and fifth thoracic vertebrae. On section it was found to consist of yellowish, granular, necrotic tissue replacing about one half of the anterior portion of the vertebrae. A large bulging mass present over the right iliac

bone consisted of similar necrotic tissue which almost completely replaced the posterior upper portion of the ilium. On the left, almost the entire ilium, including the acetabulum and a portion of the ischium, was destroyed and replaced by similar yellowish necrotic tissue. The cartilage of the head of the femur was not involved, although flowing freely in a brownish fluid pus. The anatomic neck, however, was eroded.

During removal of the brain, a large bulging mass was found anteriorly and to the left of the cerebellum. On section, yellowish necrotic material was found to replace almost the entire body of the occipital bone and the body of

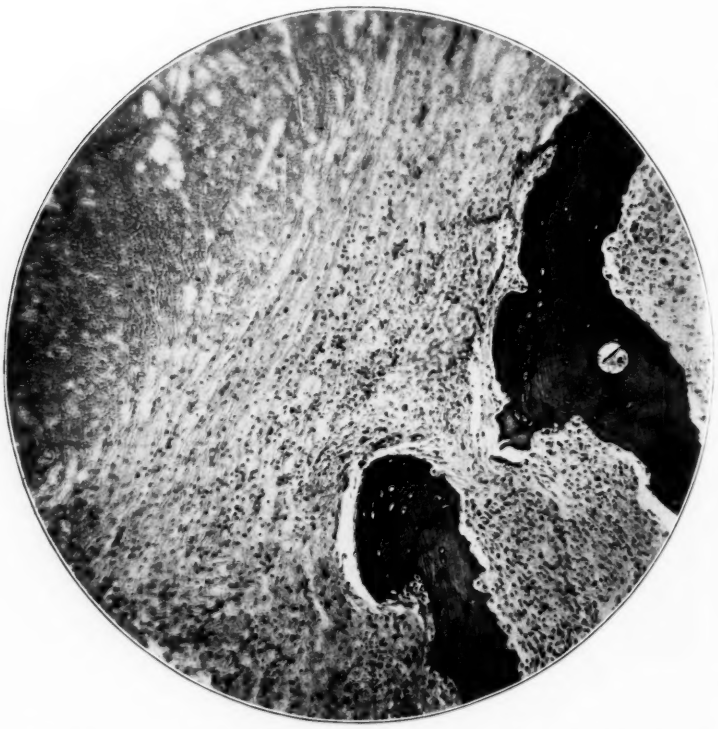

Fig. 4 (case 4).—Hodgkin's tumor mass in iliac bone showing necrosis and fibrosis.

the sphenoid. The right mastoid was filled with a greenish, purulent material. The brain, on section, did not show any abnormalities.

In addition, lesions were found in the bone marrow, pharynx muscles, pancreas, lungs, spleen and lymph nodes.

Microscopic Examination.—Many sections of lymph nodes showed combined lesions of Hodgkin's disease and lymphosarcoma. In some there was marked fibrous proliferation and endothelial cells of the Dorothy Reed type and a few eosinophils; in others, the normal architecture of the gland was destroyed, the lymphocytes closely packed, with little or no fibrosis. In all sections there were large areas of necrosis.

Comment.—The chief point of clinical interest in this case was the extensive lesions in the osseous system which were probably the first to give rise to the neurologic symptoms of pain in the shoulder and in the thigh two and one-half years before the superficial cervical lymph nodes became enlarged.

CASE 5.—A man, aged 33, was admitted to Montefiore Hospital on April 3, 1918, and died on July 21, 1918.

Fig. 5 (case 4).—Detail showing high magnification of fibrotic area in Hodgkin's disease of iliac bone.

The onset of the present illness was during the early part of 1915 with symptoms of grip followed in a few weeks by excruciating pain in the lumbar region, radiating anteriorly to the abdominal wall. The pain was intermittent and was worse at night. For a period of two years, he made the rounds of private physicians and well known hospitals. The diagnosis was doubtful, and the patient failed to obtain relief. In 1917, he was admitted to a large general hospital, where a diagnosis of focal infection was made; his tonsils were removed, and a few teeth were extracted. When improvement was not noted at the end of a few months, he was sent to Mount Clemens to be treated for supposed chronic rheumatism. There his general health improved and he

gained some weight, but his cervical lymph nodes began to enlarge. This was soon followed by a similar enlargement of his inguinal lymph nodes, accompanied by marked pruritus. He commenced to decline rapidly with signs of generalization of the condition in the chest, abdomen and possibly in the brain. A biopsy of one of the nodes showed "classical Hodgkin's disease."

Comment.—This case illustrates strikingly how Hodgkin's disease may remain clinically "localized" in an osseous region and give rise to the one neurologic symptom—pain—for more than two years before

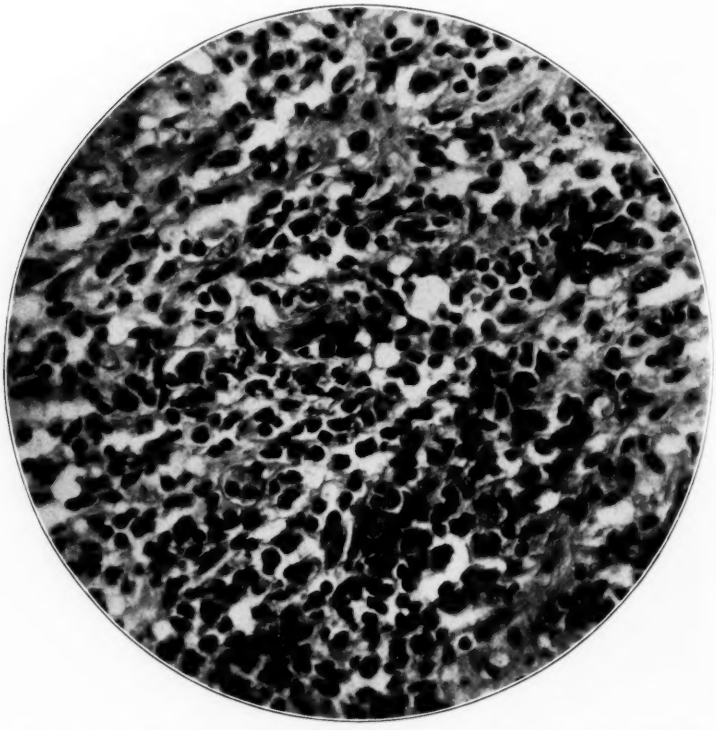

Fig. 6 (case 4).—Hyperplastic cellular stage of lymph node in Hodgkin's disease with commencing fibrosis.

the appearance of an enlargement of the lymph node and may so strongly simulate a mere local neuritis or arthritis that it may baffle detection even in an institution in which all the modern aids to diagnosis are used.

Case 6.—A woman, aged 24, referred in consultation by Dr. D. Luttinger of New York, was seen for the first time on March 22, 1924. This patient was in perfect health until January, 1923, when her friends noticed that she was los-

ing weight. For the next eight months the only other symptom present was a slowly progressive and unaccountable asthenia. In August of the same year she suddenly developed simultaneous itching of the soles of both feet. In one week this extended upward and involved symmetrically both legs to the knees. The pruritus was most intense, especially at night. This continued unabated for one month, when she was seized with violent lancinating pain commencing in the left shoulder and radiating down to the finger tips. Simultaneously with the onset of the neuralgia she felt the presence of two small lumps in the left axilla. In October, she developed severe recurring pain in the epigastrium. In November, she became jaundiced. A biopsy of one of the nodes showed Hodgkin's disease. She ran a progressive downward course, little influenced by radiotherapy. Toward the end of her life she developed herpes zoster and right facial paralysis. Autopsy was not performed.

Comment.—The most interesting feature neurologically was the appearance of simultaneous itching in both feet extending to both knees. This demonstrates how in some cases pruritus may be caused not by a local skin lesion, but by invasion or compression of sensory nerves at a distance from the site of irritation.

CASE 7.—A woman, aged 34, was admitted to the hospital on June 11, 1923, and died on April 30, 1924. In the early part of 1917, she commenced to have a dragging pain in the left upper quadrant of her abdomen. Several months later, she consulted a physician who found her spleen enlarged. The pain persisted for four years until the spring of 1921. At this time, following an acute sore throat, she developed swelling of the cervical lymph nodes followed in quick succession by similar enlargement of the axillary, epitrochlear and inguinal nodes.

In July, 1921, she was admitted to Bellevue Hospital, where a biopsy of one of the nodes showed Hodgkin's disease. From there she was referred to the Memorial Hospital, where she received radium and roentgen-ray treatments. She improved for a while until January, 1922, when she began to develop symptoms of spinal irritation. This kept growing slowly but progressively worse for the next sixteeen months. In April, 1923, a complete spastic paraplegia with sphincteric involvement was definitely established.

In June, 1923, she was admitted to Montefiore Hospital. There she ran recurring attacks of remittent fever and never recovered from her spastic paraplegia.

In July, 1923, she developed a profuse herpetic eruption, at first over the chest region on the upper right side, in the distribution of the level of the third to the fifth dorsal segment, which later spread over the entire body, giving the appearance of typical chickenpox.

Consultation with the members of the neurologic and dermatologic staff resulted in a diagnosis of Hodgkin's disease invading the posterior root ganglions, with herpes as a secondary condition.

She died with symptoms of profound asthenia on April 30, 1924.

Autopsy revealed extensive tuberculosis and retroperitoneal Hodgkin's or lymphocarcomatosis.

Comment.—Of the many features of clinical interest, I shall emphasize only the apparent primary clinical localization in the spleen four years before the appearance of superficial lymph node involvement, and the importance of treating the spine and retroperitoneum early in the development of paraplegic symptoms.

DIAGNOSTIC CONSIDERATION

A review of the literature and an analysis of thirty-six cases observed at Montefiore Hospital during the years from 1914 to 1925 provide proof of the systemic dissemination and protean manifestations of Hodgkin's disease. These studies, furthermore, furnish incontestable evidence that although in a large percentage of cases the first visible lesions occur in the superficial lymph nodes and spleen, this does not prove the primary localization in the lymph nodes, nor does primary lymph node invasion occur as frequently as is generally believed among physicians. In a considerable proportion of cases, the predominant lesions in Hodgkin's disease, as previously pointed out, apparently may occur primarily and predominantly in any tissue or organ and not only in the glands. Hence Hodgkin's disease may at times simulate a variety of local or systemic disorders and may present great diagnostic difficulties. To arrive at an early tentative diagnosis of Hodgkin's disease in the absence of any enlarged lymph nodes, a knowledge of the protean manifestations of this malignant malady is absolutely essential. In the absence of any specific diagnostic tests for Hodgkin's disease, with the single exception of the characteristic microscopic changes in the microscopic slide, which is not always obtainable, a probable clinical diagnosis can be made only on the basis of a thorough clinical history and a most complete physical examination supplemented by laboratory aids. In a differential diagnosis of Hodgkin's disease of the body cavities or the internal viscera, many diseases will have to be excluded before a probable diagnosis can be made. As the object of the present study was primarily to emphasize the protean nature and the frequency and clinical manifestations of Hodgkin's disease in the nervous system, an attempt will not be made here to enter into a discussion of the various differential diagnostic and clinical criteria of this disease. This has received extensive consideration in the publications previously mentioned, and the reader is referred to them for such information. There is one diagnostic test, however, which is considered exceedingly important to emphasize, namely, the radiotherapeutic diagnostic test. Since the appearance of the original articles of Pusey [48] and Heineke,[49] the exceeding radiosensitiveness of both pathologic and normal lymphoid tissues to radium and roentgen rays has become well known to all students of radiotherapy. The knowledge of this fact has at times been utilized by radiologists to determine whether a given tumor by its ready response to a given dose of radiation is of lymphatic constitution or

48. Pusey, William Allen: Cases of Sarcoma and Hodgkin's Disease treated by X-Ray, J. A. M. A. **38**:166 (July) 1902.

49. Heineke, H.: Ueber die Einwirkung der Roentgenstrahlen auf Tiere, München med. Wchnschr. **50**:2090, 1903; ibid **51**:785, 1904.

origin.[50] In Hodgkin's disease, before extensive fibrosis has occurred, the radiotherapeutic test can be of great help in causing a rapid and decided disappearance or diminution of the symptoms and objective signs of the disease.

A therapeutic test of this character may perhaps be objectionable in superficial enlargements or lesions when a biopsy and a microscopic slide may render a positive diagnosis. In dealing with suspected lesions of Hodgkin's disease in the internal organs or body cavities, and especially in those of the central nervous system, the radiotherapeutic test not only may determine the radiosensitiveness of the morbid process and thus give a clue to the diagnosis, but also may prove the efficient early means to prevent a paraplegia or a brain lesion.

The following case is an illustration of the efficacy of this therapeutic diagnostic test.

Case 8.—A woman, aged 27, referred by Dr. J. Axelrod of New York, was placed in my care at the Van Cortlandt Hospital on Oct. 11, 1923. She had an advanced case of Hodgkin's disease of three and one half years' duration. On admission she was markedly emaciated and anemic, with dark pigmentation of her entire body. The superficial lymph nodes were moderately enlarged. There was mediastinal and pulmonary involvement. In the upper part of the abdomen there was a large, hard, tender, immovable mass. For months before admision she had been running a remittent fever up to 103 F. Her condition was considered too far advanced for radiotherapy unless preceded by blood transfusion.

Accordingly, on Oct. 16, 1923, she was given 500 cc. of blood by the Unger method, and the next day a small dose of roentgen-ray treatment was administered to the inguinal region to test the therapeutic response and reaction to radiation. She showed slight improvement until Nov. 12, 1923, when brain involvement was evidenced by twitching of the muscles of the mouth and periods of aphasia. The next day she had a severe, generalized convulsion preceded by a loud shriek. The clonic movements lasted a few minutes and were accompanied by frothing at the mouth and biting of the tongue. For two days, the epileptiform convulsions kept recurring in severe form. Liberal doses of sedatives were administered, without result.

A diagnosis of Hodgkin's disease of the left hemisphere of the brain was made. The localization was placed in the left frontal area as suggested by the aphasia and the shriek preceding the epileptiform convulsions. In view of the general poor condition of the patient and the advanced state of the disease, it appeared probable that any recurring convulsion might lead to a fatal termination. As a last resort it was decided to try high voltage roentgen-ray treatment. Knowing the exceeding radiosensitiveness of the early and cellular lesions in Hodgkin's disease and their quick response to the intensive use of radium and roentgen-ray treatments, a full erythema dose of high voltage roentgen rays was administered to the left side of the skull in one sitting.

The technic was: voltage, 200,000,000; filtration, copper 0.5 mm., aluminum 1 mm.; milliamperes, 4; target distance, 50 cm.; portal, 15 by 15 cm.; time, 80 minutes. The reaction was profound. Within the next twenty-four hours following the irradiation, there was a drop in temperature to 97 F. with a considerable drop in pulse rate. During the remaining four weeks of the patient's

50. Blankenhorn, M. A.: Affections of the Mediastinum, Nelson's Loose Leaf Medicine **3**:578, 1920. Evans, W. A., and Leucutia, T.: Deep Roentgen Ray Exposure as an Aid in the Differential Diagnosis of Mediastinal Tumors, J. A. M. A. **85**:1215 (Oct.) 1925.

life, she had convulsions only once, on Dec. 1, 1923, during the height of excitement of a blood transfusion.

Comment.—The most outstanding point of clinical and radiotherapeutic interest in this case is the apparent response of the brain invasion to one strong therapeutic dose of the roentgen rays. The importance of high voltage roentgen-ray therapy not only as a therapeutic agent but also as a diagnostic test whenever lymphomatous or lymphosarcomatous lesions in the brain or cord are suspected was thus strikingly brought to light.

THERAPEUTIC CONSIDERATION

In any discussion of the therapy of Hodgkin's disease the following cardinal facts must be kept clearly in view:

The General Nature of Hodgkin's Disease.—As proved abundantly in the text, Hodgkin's disease is not merely a consideration of the lymphatic glands and spleen, but rather a general disease with local manifestations in different tissues and organs in different persons.

The Toxic Element in Hodgkin's Disease.—The toxic element in this disease cannot be ignored. Specific hyperplasia of the reticuloendothelial elements with or without lymphoid hyperplasia is only one phase and one stage in the pathology of Hodgkin's disease. There are now on record a great number of cases of this disease which ran an acute febrile course with toxic symptoms and then terminated fatally in from several weeks to several months. In these cases the fatal issue was caused primarily not by a proliferative compressive phenomenon, but by a severe toxemia which presented all the characteristics of an acute infectious disease.[51] Although in the chronic forms, the toxic element does not always appear strikingly in the foreground, its unmistakable presence is clearly evidenced in the frequency of the recurring attacks of pyrexia,[52] the progressive anemia and cachexia and the frequently demonstrable foci of necrosis and amyloidosis in the specific lesions of this disease.

Fibrosis and Compression Phenomena.—Extensive fibrosis of the hyperplastic lesions in the late stages of Hodgkin's disease first noted by Hodgkin himself has since been described frequently in the literature as the hard form of the disease. This extensive fibrosis may exist in

51. Heissen, F.: Zur Klinik der akuten Lymphogranulomatosis, Klin. Wchnschr. **2**:1640 (Aug.) 1923. Levy E.: Ein Fall von akuter Lymphogranulomatose in frühen Kindesalter, Arch. f. Kinderh. **75**:49 (Sept.) 1924. Hendricks, W. W.: Acute Hodgkin's Disease Following Herniotomy, Internat. Clin. **3**:217, 1921. Whillington, T. H.: Acute Hodgkin's Disease with Involvement of Internal Glands and Relapsing Fever, Quart. J. Med. **9**:83 (Jan.) 1916. Howell, A.: Acute Hodgkin's Disease, Practitioner **99**:565 (Dec.) 1917.

52. MacNalty, A. S.: Lymphadenoma with Relapsing Pyrexia, Quart. J. Med. **5**:58 (Oct.) 1911.

fairly large swellings which may press or contract on important organs or structures and give rise to irremediable or fatal compressive phenomena after the active proliferative process has become totally extinct.

Severe Anemia and Cachexia in the Advanced Stages of Hodgkin's Disease.—The toxic factor may cause a severe anemia early in the course of the disease which may simulate a frank pernicious anemia.[53] Usually, however, marked secondary anemia and cachexia indicate prolonged toxemia with severe damage to the entire hemopoietic system. This frequently is present simultaneously with extensive areas of necrosis and fibrosis in the formerly cellular and hyperplastic specific lesions.

Etiology in Hodgkin's Disease Unknown.—Nearly a century after Hodgkin's first description of the disease, its etiology still remains obscure, and a specific form of treatment has not been discovered.[54]

Chemotherapy and surgical intervention, which have been tried out extensively for a number of decades, have proved disappointing either as curative or palliative measures. The most efficient local treatment for Hodgkin's disease universally recognized today is of radium and the roentgen-ray treatment. The effect of both of these forms of radiant energy is prompt and efficient in influencing the cellular proliferative manifestations of this disease. Even bulky growths and infiltrations have been noted to disappear or regress promptly under radiotherapy, with great symptomatic relief not only of the compressive phenomena but at times also of the accompanying toxemia.

Although permanent cure has not been reported, prolongation of life for many months and years has been noted by many observers.[55]

53. Halix, O. (footnote 34).

54. Lubarsch, O.: Die Lymphogranulomatose, Aschoff's Path. Anat. **2**:578, 1923. Kaufmann, E.: Lymphogranulomatose, Path. Anat., Berlin-Leipzig **1**: 203, 1922. Ewing: Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1922. Cunningham, W. F.: The Status of Diphtheroids with Special Reference to Hodgkin's Disease, Am. J. M. Sc. **153**:406 (March) 1917. Beifeld, A. F.: Present Status of Hodgkin's Disease, Am. J. M. Sc. **155**:409 (March) 1918. Cunningham, W. F., and McAlpin, K.: Experiments with Hodgkin's Disease; An Attempt to Produce it in Anthropoids and Other Monkeys, Arch. Int. Med. **32**:353 (Sept.) 1923. Lemon, W. S.: Tuberculosis as an Etiological Factor in Hodgkin's Disease; A Historical Review, Am. J. M. Sc. **167**:178 (Feb.) 1924. Stewart, M. J., and Dobson, J. F.: Inoculation and Implantation Experiments in Monkeys with Glands from cases of Hodgkin's Disease, Brit. J. Exper. Path. **5**:65 (April) 1924.

55. Simmons, C., and Benet, G.: A Report on the Cases Observed at the Collis P. Huntington Memorial Hospital from April, 1913, to July, 1916, with Special Reference to Treatment with Radium and X-Rays, Boston M. & S. J. **177**:819 (Dec.) 1917. Levin, I.: Action of Radium and Roentgen Rays on Normal and Diseased Lymphoid Tissue, J. A. M. A. **77**:930 (Sept.) 1921. Schreiner, B. F., and Mattick, W. L.: Radiation Therapy in 46 Cases of Lymphogranuloma (Hodgkin's Disease), Am. J. Roentgenol. **12**:133 (Aug.) 1924. Stone, W.: Treatment of Hodgkin's Disease by X-Ray and Radium Based Upon a Study of 200 Cases, Canad. Pract. & Rev. **59**:109 (March) 1924.

(Footnote continued on following page)

However, to obtain the best results with radium and the roentgen rays, radiotherapy must be properly and efficiently applied in the early soft or cellular stages before toxic degeneration has caused extensive fibrotic changes which have converted the lesions of Hodgkin's disease into dense hyaline masses that are just as resistant to radiation as old scar tissue. In lesions of the nervous system especially, prolonged or severe mechanical compression alone even without an accompanying toxic process may result in destructive irremediable degenerative changes.

A fair demonstration of what radiation therapy may achieve in some cases in which paraplegia is present was recently reported by Weber.[42] A patient with Hodgkin's paraplegia was treated with roentgen rays over the site of the lesion. The paraplegia cleared up completely and did not recur within the next five years.

The following two cases are a further illustration of the possibilities and limitations of radiotherapy in Hodgkin's disease with neurologic symptoms:

CASE 9.—*History.*—A man, aged 46, was referred to the radium clinic of Montefiore Hospital on Feb. 6, 1924, with a diagnosis of Hodgkin's disease proved by biopsy. In the early part of 1921, he commenced to have burning and pressure pain in the epigastrium aggravated by food intake. Gradually he began to feel weak but did not lose any weight until the end of 1923. At this time he developed severe pain in his upper dorsal spine and noted bilateral enlargement of the axillary nodes. He consulted a physician, who detected sugar in his urine. A diagnosis of diabetes was made, and no significance was attached to the enlarged lymph nodes in the axilla. Shortly afterward the cervical and inguinal lymph nodes also began to enlarge. He began to lose weight and strength rapidly, and developed a generalized pruritus.

Examination.—On physical examination the patient was pale and slightly undernourished. All the external superficial lymph nodes were greatly enlarged and in places matted. The result of examination of the chest, lungs and heart was negative. Abdominal examination revealed enlargement of the liver to about 5 cm. below the costal margin. The spleen and kidneys were not palpable.

Blood examination revealed: red blood cells, 3,520,000; white blood cells, 4,700; polymorphonuclears, 66 per cent; lymphocytes, 28 per cent; eosinophils, 3 per cent; myelocytes, 3 per cent. The blood Wassermann reaction was negative. The blood sugar content was 96 mg. per hundred cubic centimeters; urea, 17.1 mg.; uric acid, 3.1 mg. Examination of the urine was negative for glucose and albumin.

Treatment and Course.—On Feb. 11, 1924, high voltage roentgen-ray treatment was started and continued until Dec. 29, 1924. Altogether forty-four one-half erythema doses were given, averaging forty minutes a treatment.

In April, 1924, the patient developed pain in the lumbosacral region radiating down both lower extremities to the ankles. His legs felt weak. He walked

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Bowing, H.: Value of Radium and X-Ray Therapy in Hodgkin's Disease, J. Radiol. **2**:20 (Dec.) 1921. Desjardins, A.: Radiation Treatment of Hodgkin's Disease with Particular Reference to Mediastinal Involvement, J. Radiol. **1**:161 (Nov.) 1923. Chaoul, H., and Lange, K.: Ueber Lymphogranulomatose und ihre Behandlung mit Röntgenstrahlen, München. med. Wchnschr. **70**:725 (June) 1923. Klewitz, F., and Lullies, G.: Beitrage zur Prognose des malignen Granuloms, Strahlentherapie **19**:1058, 1924. Desjardins, A., and Ford, F. A.: Hodgkin's Disease and Lymphosarcoma, J. A. M. A. **81**:925 (Sept.) 1923.

with a stiff, shuffling gait suggestive of an osseous lesion of the lower part of his spine. There was some tenderness over the lumbosacral region. Gradually, however, as radiotherapy was persisted in, all the symptoms and signs of the disease retrogressed.

Roentgen-ray treatment was discontinued on Dec. 29, 1924. The patient was reexamined on Dec. 6, 1925. He felt greatly improved in health and strength. During the past six months, he has worked regularly at his former occupation as a painter and has felt well and strong. There has been no reappearance of the superficial glandular swellings. He does not suffer from respiratory symptoms. He can walk up several flights of stairs without dyspnea. Examination of the urine in July, 1925, failed to show any evidence of glucose, although he had been on a full nonrestricted diet for many months prior to examination.

Physical reexamination revealed moderate pallor but no dyspnea, cyanosis or edema. He could stoop forward and touch his toes without discomfort. The superficial lymph nodes were only slightly enlarged, discrete and hard. The heart showed slight acceleration but no other abnormalities. The lungs and abdomen apparently were normal.

CASE 10.—*History.*—A man, aged 46, was referred to the radium clinic of Montefiore Hospital on Aug. 29, 1923, with a diagnosis of Hodgkin's disease, corroborated by biopsy of a lymph node. In August, 1920, three years before admission, he commenced to have pain in both lower extremities on walking. This became progressively worse in character until May, 1923, when he began to suffer from severe upper abdominal pain, cutting in character, radiating posteriorly to the spine. Simultaneously with the onset of his symptoms, he gradually lost weight and strength and became dyspenic on exertion.

Examination.—The patient was slightly cachetic and emaciated, moderately pale and cyanotic. All the superficial lymph nodes were greatly enlarged, presenting huge conglomerated masses. The parotid and submaxillary salivary glands shared in the pathologic process. Mediastinal involvement was elicited on physical examination and corroborated by roentgenograms. In the upper part of his abdomen there was a large, hard, immovable, tender mass, showing invasion of the retroperitoneal lymph nodes. The liver extended 4 cm. and the spleen 8 cm. below the costal margin. The patient walked with a shuffling gait as though he had lost the flexibility of the lower part of the spine.

Blood examination revealed: red blood cells, 4,800,000; white blood cells, 10,000; hemoglobin, 50 per cent; polymorphonuclears, 68 per cent; lymphocytes, 28 per cent, eosinophils, 4 per cent. The blood Wassermann test was negative.

Roentgen-ray examination of the spine was negative.

Treatment and Course.—Immediately after admission, high voltage roentgen-ray treatment was started and carried out systematically over the cervical, axillary, inguinal, mediastinal and abdominal regions and over the entire spine. During a period of sixteen months, until Jan. 19, 1925, he received altogether fifty-two treatments, each averaging forty minutes. The result was a gradual retrogression of all the lymph nodes and the liver and splenic enlargement. There was moderate recession of the neurologic symptoms and apparently no further progress of the involvement of the nervous system.

The patient was reexamined on Dec. 6, 1925, almost eleven months after the last roentgen-ray treatment. His general condition was fair. He presented no definite enlargement of his lymph nodes. His heart, lungs and abdomen apparently were normal. His liver and spleen were not enlarged. His chief complaints were still neurologic: pain and weakness of both lower extremities. In spite of his subjective complaints, he was able to be up and about and could stoop forward and touch his toes without difficulty.

Comment.—As important as the recognition that efficient radiotherapy in Hodgkin's disease can be carried out only in the cellular

hyperplastic stage of the disease is the knowledge that this malady is protean and general in its manifestations. The successful attack on one hyperplastic proliferative focus means only greater vigilance for the stealthy appearance of other pathologic foci in the same or distant regions, tissues or organs of the body. A patient with Hodgkin's disease should remain constantly under expert medical and radiotherapeutic supervision, and the hyperplastic lesions should be treated in their incipiency. Only by such close vigilance can the life of the patient best be prolonged and safeguarded. Any general measure must not be neglected, such as dietetic, hygienic or tonic, which will enable the patient to make a more or less successful fight against this malignant disease.

CONCLUSIONS

Hodgkin's disease should no longer be defined as a specific enlargement of the lymph glands and spleen with occasional deposits in other viscera accompanied by a severe secondary anemia. It is a specific malignant general disease with protean manifestations in which any tissue or organ in any region of the body may become clinically, primarily and predominantly affected. Pathologically, Hodgkin's disease is characterized by a specific hyperplasia of the reticulo-endothelial elements wherever the invasion of the morbific agent or process occurs. Since the reticulo-endothelial system is coextensive with the entire body [56] and is not confined merely to, although predominant in, the lymphohemopoietic system, Hodgkin's disease may arise primarily, pathologically as well as clinically, anywhere in the body tissues. The cellular proliferative stage of Hodgkin's disease is only one phase and one stage of the morbid process. Regressive changes—necrosis and fibrosis—are invariable later stages in the development of the disease. Toxemia and anemia are the usual accompaniments of the disease at any stage, although they are most marked as the disease process advances.

The invasion of the nervous system in Hodgkin's disease is by no means as rare as textbooks would lead one to believe. A review of the literature and my own cases have shown that the nervous system may become clinically, primarily and predominantly affected and give rise to symptoms for months and years before the occurrence of any demonstrable enlargement of the lymph nodes or spleen. In a series of thirty-six patient with Hodgkin's disease observed at Montefiore Hospital during the years 1914 to 1925, ten patients, or 27.7 per cent, showed invasion of the nervous system.

Early diagnosis of Hodgkin's disease of the nervous system can be made only on the basis of a thorough and complete study of all the clinical signs and symptoms present in a given case. A neurologic

56. Aschoff, L.: Lectures on Path., New York, Paul B. Hoeber, 1924, p. 1.

examination alone, supplemented even by various laboratory tests directed exclusively toward the nervous system, may prove insufficient to establish a diagnosis. In doubtful cases, therefore, the radiotherapeutic test may prove an important aid in diagnosis. The lesions in Hodgkin's disease before extensive degenerative changes and fibrosis have set in are exceedingly radiosensitive. A quick subsidence of pressure phenomena not only may give a clue to the diagnosis, but also may relieve the patient of an early paraplegia or a brain lesion.

Early diagnosis in Hodgkin's disease of the nervous system is essential to prevent irremediable degenerative changes in the nervous elements.

Radiotherapy, which is the chief measure in the treatment of this malignant disease, must be used early, for in the late fibrotic stages its efficacy is nil. When used early and effectively, it may relieve a paraplegia which may never recur, and thus spare the patient from a condition of incontinence and bed sores lasting through many months if not years.

PAIRED AURICULAR EXTRASYSTOLES

SIMULATING INTERPOLATED EXTRASYSTOLES OF SUPRAVENTRICULAR ORIGIN *

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An electrocardiogram (fig. 1) was recently obtained, which on first examination appeared to contain interpolated extrasystoles of supraventricular origin. Since such an occurrence, as far as I am aware, has not been demonstrated and furthermore is theoretically impossible, the tracing has been examined more carefully, and a different interpretation has been made.

In an article on interpolated extrasystoles, Myers and White [1] state:

> An interpolated beat is a premature contraction of the ventricles which is not followed by a compensatory pause and does not disturb the dominant rhythm of the heart. It is impossible for auricular beats to be interpolated, because auricular premature beats are bound to disturb the dominant rhythm.

One must take exception to the latter phrase, for occasionally one finds auricular premature beats followed by a full compensatory pause.[2] In these instances the auricular premature beat must be so late, and the point from which it rises so distant from the sino-auricular node that the contraction passing over the auricle from this abnormal (ectopic) impulse center fails to reach the sino-auricular node before the latter has started a contraction wave. The two waves meet somewhere in the auricular tissue and come to an end. Meanwhile the sino-auricular node, which has, as is said, discharged itself, proceeds to build up new impulse material at the rate then obtaining in the heart, and starts the following contraction wave at exactly the time it would have if extrasystole had not occurred. Thus the pause is fully compensatory, and the dominant rhythm of the heart is undisturbed.

I do agree, however, with the assertion [1] that interpolated extrasystoles must be ventricular in origin, and that they do not disturb the dominant rhythm of the heart. In the rare instance of an auricular extrasystole which does not disturb dominant rhythm it does, however, take the place of one of the normal contractions, and the tracing shows

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* From the Evans Memorial.

1. Myers, M. M., and White, P. D.: Interpolated Contractions of the Heart with Especial Reference to Their Effect on the Radial Pulse, Arch. Int. Med. **27**: 503 (April) 1921.

2. Reid, W. D.: The Heart in Modern Practice, Philadelphia, J. B. Lippincott Company, 1923, pp. 59 and 199. Lewis, T.: The Mechanism and Graphic Registration of the Heart Beat, New York, Paul B. Hoeber, 1920, p. 221.

merely a single late occurring auricular premature beat. There is not, therefore, a true extra beat, and so no interpolation.

The electrocardiogram (fig. 1) shows in leads one and three single instances of runs of three beats which are sufficiently close together to give the central beat the appearance of being interpolated, but an accurate measurement shows that the space (time) between the first and third beats of the run is greater than the sum of any two normal beats, and it is greater than can be accounted for by the slight prolongation of the P-R interval of the third beat. It is evident, therefore, that the last beat in each of these groups occurs at a slightly later time than it should if extrasystole had not occurred. The dominant rhythm is,

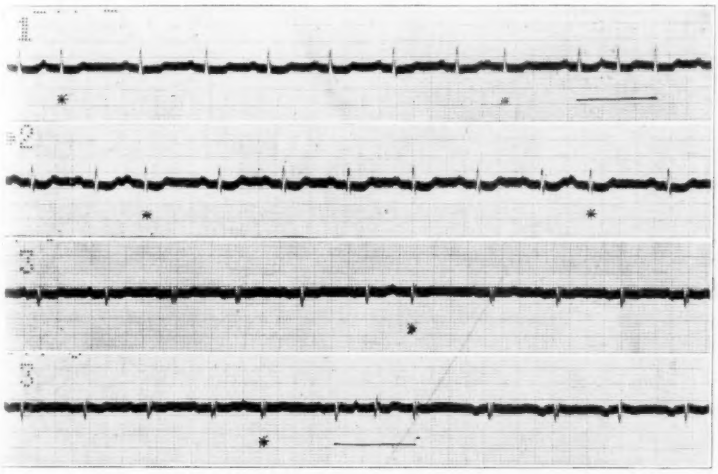

Fig. 1.—The two runs of three beats, discussed in the text, are indicated by the horizontal line placed below; the single auricular extrasystoles occurring elsewhere in the tracing are marked by an asterisk. The third and fourth strips are from lead 3 and are continuous, the upper being the first half. Coarser abscissas mark off periods of one-fifth second; the finer, of one twenty-fifth second.

therefore, disturbed and, if the criterion that dominant rhythm is not disturbed holds for interpolated extrasystoles, there is, in this electrocardiogram, no true interpolation.

Lead 1 shows two instances of auricular premature beats followed by pauses which are not fully compensatory. Immediately after the pause successive to the second premature beat follows the run of three beats, which makes this lead of interest. The first of the three beats appears to be normal. The second is clearly an auricular premature beat since it is preceded by a P wave that is premature; in fact, it is

superimposed on the T wave of the first member of the group of three beats. The origin of the third beat is less easy to determine. It is introduced by a P wave which is superimposed on the T wave of the preceding heart cycle, and the contour of this P + T wave is such as to prevent a positive decision between the normal and an ectopic point of origin. The P-R interval is lengthened, as is common after interpolated extrasystoles, but this does not favor either point of origin. The beat immediately following this third beat of the run occurs at exactly the normal interval. (This measurement is obtained from the respective P waves since the variation in the P-R intervals disturbs the time of the ventricular complexes.) If this is a premature beat, it is an instance in which the point of origin is so near the sino-auricular node that the latter is discharged practically at once and builds up the material for the succeeding contraction in the usual time.

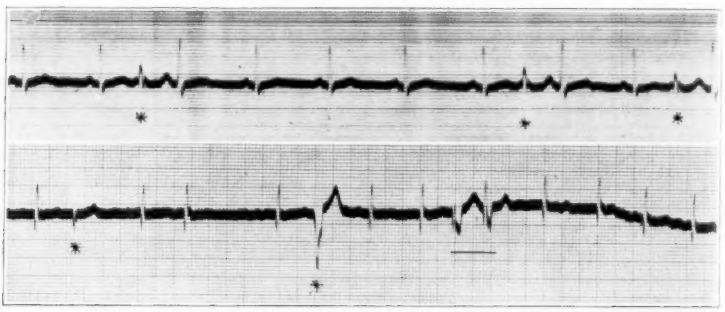

Fig. 2.—The upper part shows three instances of interpolated extrasystoles, marked by an asterisk. The time marker, it will be noted, was not in operation, but the interpretation of the tracing is not impaired thereby. The lower part shows paired ventricular extrasystoles indicated by a horizontal line placed below, in a tracing of auricular fibrillation. Two single extrasystoles are marked by an asterisk. Time marker as in figure 1.

Lead 3 contains a somewhat similar run of three beats, the interpretation of which is similar to that applying to lead 1, except that the run occurs just at the time of the change from normal to a slower rhythm, probably from the auriculo-ventricular node. Of the three beats of the run I should consider the first one due to the simultaneous contraction of auricular waves starting from the sino-auricular and auriculo-ventricular nodes, respectively. The second appears to be an auricular premature beat and the third is doubtless subject to the same explanation as that given for the third beat in the run noted in lead 1. The slight aberration of the Q.R.S. complexes causes less concern when one notes that similar variations occur elsewhere in lead 3.

The alternative interpretation, namely, that these two runs are really examples of the interpolation of auricular premature beats, may seem more plausible to some readers. It will be found, however, that the third beats were somewhat delayed from their time of expected occurrence when the premature was interpolated. This delay exceeds that explainable on the prolongation of the P-R interval and is rather greater than would appear likely when one adds the factor of sinus arhythmia, which happens to be present to a slight degree in this electrocardiogram. The interpolation conception forces one to believe that the second wave, the auricular premature, affected the sino-auricular node only in slightly delaying one of its impulses. This seems too difficult to reconcile with

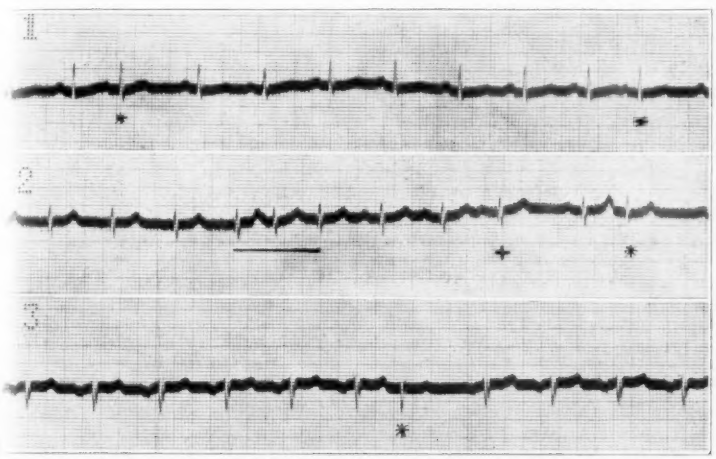

Fig. 3.—Tracing obtained two months after that in figure 1. The asterisk and horizontal line are used as in figure 1. Note the run of three beats in lead 2, the disappearance of the depression of the T wave and the return of the P-R interval to normal. Time marker as in figure 1.

cardiac physiology pertaining to premature beats, for it seems accepted that auricular premature beats take the place of one of the beats of the normal rhythm, and the postextrasystolic pause is never less than that following a beat of the normal dominant rhythm. A rare exception to the latter statement occurs in some instances in which the premature beat is near or at the S-A node, and the succeeding heart beat occurs following a diastole slightly less than the normal. It has been suggested [3] that impulse formation has been stimulated so that the S-A node initiates

3. Lewis, T.: Observations upon Disorders of the Heart's Action, Heart **3**:279 (June) 1912.

a contraction more rapidly, not so early as happens in the electrocardiogram (fig. 1) discussed in this article, however.

Figure 2 is introduced to illustrate an instance of true interpolation of a premature beat and to show by contrast how unhesitatingly one may recognize paired extrasystoles if they are of ventricular origin.

The history of the patient from whom this electrocardiogram was obtained may be summarized as follows:

A woman, aged 64, who was seen in the Outpatient Heart Clinic, had a condition diagnosed tentatively as auricular fibrillation. She was short of breath for about three minutes after ascending one flight of stairs; she walked without untoward symptoms. She said that her health had been satisfactory until recently, and that she did not recall any diseases of etiologic significance regarding involvement of the heart. She had been overweight for years; her present weight was 190 pounds (86.2 Kg.); her height was five feet, six inches.

Physical examination showed an obese chest wall, a cardiac impulse just palpable in the fifth interspace at left midclavicular line, no enlargement detected by percussion, no murmurs and marked irregularity in rhythm. The apex rate was 76, wrist 66 and pulse deficit 10. Edema of the legs was not present. The tentative diagnosis was auricular fibrillation.

Treatment and Course.—Digitalis was prescribed (modified Eggleston method). One week later there was slight nausea, and digitalization appeared complete. The heart showed one and two sound premature beats occurring every four, six, eight or more beats in what appeared to be a regular rhythm. The diagnosis was changed to normal rhythm interrupted by frequent premature beats and digitalis was omitted. An electrocardiogram was taken (fig. 1).

Subsequent observation showed the patient to be doing well without digitalis and on a diet rich in vitamins and sufficiently low in calories to induce a gradual reduction in weight.

An electrocardiagram (fig. 3) was taken two months later. The disappearance in the depression of the T wave and the shortening of the P-R interval to normal were evidently caused by the absence of digitalis action on the heart. The fact that another run of three beats was disclosed in lead 2 is evidence that this feature is not dependent on digitalis for its presence.

SUMMARY

An electrocardiogram is published which at first sight appears to depict interpolated extrasystoles of supraventricular origin.

The interpretation of this tracing is discussed, and the difficulty in differentiating between a true interpolation and pairing of auricular extrasystoles is pointed out.

Book Reviews

SCHISTOSOMIASIS VEL BILHARZIASIS. By C. G. KAY SHARP, M.D., with a foreword by J. B. CHRISTOPHERSON, C.M.G., M.D. Price, $2.75. Pp. 74. New York: William Wood & Company, 1925.

Schistosomiasis, the proper title for the condition formerly included under the name bilharziasis, is fortunately rare in North America, but in Asia and Africa it is still a formidable disease. As Dr. Christopherson says, it is one of the great endemic diseases of the world, and anything that will emphasize the importance of the parasites and their effects in the minds of the public should aid in the control of the infestation. The work under review admirably answers the needs. Dr. Sharp gives a brief but adequate historical account. Bilharz deserves credit for the discovery, and the reason his name is no longer applied to the disease is that some time before Cobbold proposed it, Weilland had named the genus as now recognized by zoologists.

Three disease groups are caused by these trematodes: urinary schistosomiasis, due to *Schistosoma hematobium;* intestinal schistosomiasis due to *S. mansoni*, and schistosomiasis of the Far East, often pulmonary, due to *S. japonica*. Dr. Sharp pays special attention to urinary schistosomiasis with which he became familiar in Natal, where many cases occur in natives and Europeans. The intermediate hosts are water snails, and the steps in the discovery of the life cycle are well described by the author.

In the hematuric form, ova are discharged in large numbers in the urine, especially in the morning, and at the end of micturition. As they are 0.16 mm. in length and 0.06 mm. in breadth, they can be seen with the naked eye. Each ovum already contains the miracidium, and can be quickly hatched in water at 120 F. The miracidium is ciliated, elongated when in motion and tends to become spherical when stationary. They can hatch in the bladder when the urine is diluted, as after taking a glass of beer. Given an opportunity, the miracidia enter the bodies of water snails, become sporocysts, and form daughter cysts in which cercaria develop. The maximum development occurs in the liver of the snail, which may be filled with cercaria. These can be seen wriggling in the sporocysts. They require about six weeks for full development, and when that occurs, they bore their way through the tissues of the snail into the respiratory organs or the intestinal canal and so reach the water. Dr. Sharp gives brief but clear descriptions of the pathologic change and morbid anatomy of the various forms of schistosomiasis. Cirrhosis of the liver is one of the most interesting, and the cases seem to give a high percentage of primary carcinoma. Little is known of immunity. The signs and symptoms are fully described. The definite diagnosis depends on the discovery of the ova in the urine. The author uses a concentration method, pouring off the water after successive centrifugalizations. Death is rare, the disease continuing for months with little inconvenience to the patient; it may even last for many years. Septic diseases and malignant changes are not infrequent. Living ova may be expelled during the entire period of infection, having been found by Christopherson as long as twenty-eight years after its beginning.

The author gives a general review of the treatment of schistosomiasis in different parts of the world. Mass treatment by antimony tartrate is a valuable prophylactic, but education to check infection and reinfection and destruction of infected snails should be attempted. Dr. Sharp gives selected references to the extensive literature. The book is well printed on good paper. The few illustrations are adequate, but the price seems to set a record for seventy-four small octavo pages. This would seem to lessen the circulation of a work that should be in the hands of health officers and practicing physicians over a

large part of the world. It would seem more economical to publish such works in periodicals or reports of institutions.

THE PHYSIOLOGY OF THE CONTINUITY OF LIFE. By NOEL PATON, M.D., B.S.C., LL.D., F.R.S., Regius Professor of Physiology, University of Glasgow. Pp 226, with subject and author index, and 78 illustrations. London: The Macmillan Company, Limited, 1926.

This is a short monograph on the physiology of reproduction and inheritance from the standpoint of a physiologist. The book is based on lectures delivered to the students in physiology in the University of Glasgow during the past five years. The author assumes that the reader has some knowledge of chemistry, zoology and general physiology. He presents and attempts to criticize and analyze theories and facts in the large and important fields of inheritance and reproduction. He says in the preface: "In every branch of physiology there is the tendency to give and accept *ex cathedra* teaching, which is soul destroying alike for the teacher and the student. Perhaps in no part of physiology is the tendency to authoritative teaching more seen than in that which concerns reproduction and inheritance. Certain conclusions have been generally accepted as *choses jugés*, about which further discussion is deemed unnecessary, but, upon examination, many of them are found to be mere hypothesis. The dictum that life can only arise from life, the so-called mendelian laws of inheritance, the part played by chromatin in inheritance and in the determination of sex and the impossibility of the transmission of acquired characters may be cited as examples."

This quotation gives a clear idea of the author's point of view throughout the monograph. He does not always seem successful, however, in carrying this view into operation, at least the success of the author varies greatly in the different chapters.

The book is divided into nine chapters on life and heredity, reproduction, sex, the determination of sex (two chapters), the relationship of the germ cells to the somal cells, the influence of the gonads on the soma, the influence of the soma on the gonads, sexual life, the nutrition of the zygote before birth (pregnancy), parturition, the nutrition of the infant — suckling and milk secretion. These chapters are of unequal value in completeness of statement and in critical evaluation of the data. For example, the chapter on parturition seems incomplete, both in statement of facts, in description of processes and in analysis of factors involved. The volume nevertheless brings together scattered data in the fields of botany, zoology, physiology and internal medicine in a helpful and lucid presentation. The volume will be of value to physicians and other students of the biologic sciences.

MODERN MEDICINE, ITS THEORY AND PRACTICE, IN ORIGINAL CONTRIBUTIONS BY AMERICAN AND FOREIGN AUTHORS. Edited by SIR WILLIAM OSLER; ed. 3 revised. Re-edited by THOMAS MCCRAE, assisted by ELMER H. FUNK. Volume 3. Pp. 1052 with illustrations. Price, $9. Philadelphia: Lea & Febiger, 1926.

This volume contains a series of excellent articles thoroughly revised to date on the diseases of metabolism and the digestive system. The chapter on metabolism by Eugene F. Du Bois is of especial value to the practitioner. The scientific data of this broad and still incomplete subject are presented so clearly as to be readily grasped by the average clinician. The chapters on diabetes, diabetes insipidus and gout by Thomas F. Futcher are authoritative and complete. A general discussion by Charles G. Stockton of the physiologic and anatomic factors which enter into an understanding of the diseases of the digestive tract opens the section devoted to gastro-intestinal diseases. The splendid chapter on the diseases of the mouth and salivary glands originally written by David Riesman has been revised by Henry K. Mohler. The chapters

on diseases of the esophagus by Chevalier Jackson and Louis H. Clerf, on functional diseases of the stomach by Julius Friedenwald, on organic diseases of the stomach by Charles F. Martin and Colin Sutherland, on diseases of the intestines by Alfred Stengel and on diseases of the pancreas by Eugene L. Opie are likewise authoritative and complete. The chapter on diseases of the liver, gallbladder, and biliary ducts by the late A. O. J. Kelly, has been revised by B. B. Vincent Lyon. It contains much of interest concerning the function of the liver and gallbladder; a discussion of the various functional tests of the liver, including the van den Bergh test, is included. The discussion of nonsurgical drainage of the biliary tract is of interest, although the diagnostic and therapeutic value of this procedure is questioned by many internists, because of the author's position as the foremost advocate of its use. Only a short paragraph is devoted to cholecystography as developed by Graham, a method which has clarified the diagnosis of gallbladder disease in a remarkable manner, and which is among the foremost achievements of medicine during the past decade. The admirable chapter on sprue by Edward Jenner Wood should be read by all American physicians, since the disease occurs in this country, is little known, and since it is likely to be confused with pernicious anemia. The original chapter on diseases of the peritoneum by Sir Humphrey Rolleston has been revised and remains an excellent portrayal of this subject. The volume, on the whole, maintains the high Oslerian standard set for the complete work and deserves a place in every medical library.

ABHANDLUNGEN AUS DEM GESAMTGEBEIT DER MEDIZIN. DER HEUTIGE STAND DER LEHRE VON DEN GESCHWÜLSTEN. By CARL STERNBERG. Price, 65 cents. Pp. 136, with 21 illustrations. Second edition. Vienna: Julius Springer, 1926.

This second edition of Sternberg's brief manual is one of a number of similar works by members of the faculty of the University of Vienna. A little more than one-half is devoted to the general subject and the remainder to a brief account of separate varieties of tumors.

Both portions are complete, well written and carefully epitomized to handbook proportions. The work is so modern that the recent and somewhat sensational work of Gye has a judicial and judicious review. The work of a few American investigators receives creditable mention. Omissions of any reference to other American work, that by Mallory on dural fibromas, for example, is in thorough accord with the general failure of European writers to consider American research; this neglect, however, is not so marked as in former years. The monograph on melanomas by the English pathologist Dawson is not mentioned.

In the second portion, the care with which undecided matters are dealt is highly satisfactory. As examples, the origin and classification of growths such as the small yellow epithelial tumors of the appendix so opprobriously named "cancroid" and the tumors thought to be primarily from the peritoneum may be cited. Sternberg states definitely that the leukemias, lymphogranulomatosis, chloromas and myelomas are not to be regarded as tumors (blastomas).

The illustrations are carefully selected and are only of gross appearances. The bibliography is a rich mine of "source-material" for a work so abridged. Students who read German will find pleasure in this account of tumors as well as a large amount of authoritative information concisely stated.

COLLECTED PAPERS, HENRY FORD HOSPITAL, DETROIT, MICH. Price, $8. New York: Paul B. Hoeber, 1926.

Like any book compiled of collected papers, this volume contains many current articles on more or less unrelated subjects. The main portion of the work is comprised of forty-three articles by members of the staff of the Henry Ford Hospital covering a period of ten years, from 1915 to 1925. With few excep-

tions, notably the articles by McClure on "The History of Transfusion of Blood" and "Pernicious Anemia," the contributions are taken from the recent literature. The major portion of the work which is presented in some of the articles was done at institutions other than the Henry Ford Hospital. In nearly all instances, the articles are reprinted from journals of well recognized high standing, so that many of them have been reviewed previously.

The contribution by Davidson on "Tannic Acid in the Treatment of Burns" is worthy of special note. His conclusions are conservative and seem to be well warranted by the theoretical and practical evidence presented. The preliminary report on "Immediate Metabolic Disturbances Following Deep Roentgen-Ray Therapy" by Doub, Bolliger and Hartman, has, in the light of subsequent contributions, been the basis for some new and rather promising developments. The work of Mason and others on tissue extracts and tissue autolysis, and that of Plass and his associates on blood chemistry in the toxemias of pregnancy, form two groups of interesting and helpful papers.

As a whole, it seems that the articles contained in this volume compare favorably with other similar collections.

HISTORY TAKING AND RECORDING. By JAMES A. CORSCADEN. Pp. 78. Price, $1.50. New York: Paul B. Hoeber, 1926.

Any method that may serve as a stimulus to better history taking and recording is of particular interest to those concerned with the teaching of physical diagnosis. Mastery by the student of the technic of history taking is of such great importance that many attempts to clear the way have been made through the medium of handbooks. This text of seventy-eight pages designed for the student includes a discussion of the general principles of case history writing and an extensive list of terms employed, classified according to the regions of the body and the diseases commonly located in those regions. Suggestions as to form and outline should clarify the objective sought in a reliable history; so far as they are stimulating to the student, they will serve a useful purpose. Since, however, a medical history reflects the general medical experience and attainments of a physician, a handbook cannot entirely solve this problem. This little book should be as valuable as any in providing the foundation for a good history.

THE SURFACE EQUILIBRIA OF BIOLOGICAL AND ORGANIC COLLOIDS. By LECOMTE DU NOÜY. American Chemical Society Monograph Series. Pp. 212. Price, $4.50. New York: Chem. Catal. Co., 1926.

This monograph by du Noüy with introductions by Alexis Carrel and Robert A. Millikan, concisely presents eleven chapters on surface equilibria as follows: technic; drop of the surface tension of colloidal solutions as a function of time; monomolecular layer of serum constituents; sodium oleate; egg albumin; characteristics of immune serum; influence of colloids on the crystallization of sodium chloride; surface equilibrium of complex colloidal solutions; interfacial tension; colloidality of solutions of proteins, serum and plasma; general conclusions. That a monograph has won the approbation of so eminent a physicist and biologist, stamps it as a contribution of first rank. Although all of the applications of this work may not be apparent now, the author in quoting from Claude Bernard, does "open up a new road."

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CONTENTS

PAGE

Hypertension in Pregnancy: Relation of the Calcium Content of the Blood to the Etiology. Edward J. Stieglitz, M.D., Chicago 465

Vital Capacity: A Study of the Effect of Breathing Dry Air. R. D. Leas, M.D., Cleveland 475

Intravenous Injection of Ouabain in Man. John Wyckoff, M.D., and William Goldring, M.D., New York 488

House Dust in the Etiology of Bronchial Asthma and of Hay-Fever. Albert H. Rowe, M.D., Oakland, Calif. 498

The Value of Histamine as a Test for Gastric Function. H. L. Bockus, M.D., and Joseph Bank, M.D., Philadelphia 508

The Course of Hyperthyroidism Under Iodine Medication. Paul Starr, M.D., Chicago 520

Cardiac Changes Subsequent to Experimental Aortic Lesions. J. A. E. Eyster, M.D.; Walter J. Meek, Ph.D., and F. J. Hodges, M.D., Madison, Wis. 536

Chronic Acidosis in Rabbits and in Dogs, with Relation to Kidney Pathologic Change. Beatrice Carrier Seegal, M.D., Boston 550

Hemorrhagic Focal Gastroduodenal Lesions: Preliminary Report of Three Cases. Andrew B. Rivers, M.D., Rochester, Minn 564

Hodgkin's Disease, with Predominant Localization in the Nervous System; Early Diagnosis and Radiotherapy. Solomon Ginsburg, M.D., New York 571

Paired Auricular Extrasystoles Simulating Interpolated Extrasystoles of Supraventricular Origin. William D. Reid, M.D., Boston 596

Book Reviews 601